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Regulatory Rapporteur

The international journal for professionals in regulatory affairs

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text mining and curation

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*Exploring topics ranging from new US FDA guidances
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JAN 2021 – JAN 2022

Regulatory Rapporteur focuses each month on a specific topic (special features), publishing a selection of articles on that topic. In addition, each issue carries a range of standalone articles – topics of particular interest to our readership that do not fall into any of our planned special features categories.

If you would like to submit an article, upcoming focus topics are shown below. Standalone articles on any relevant healthcare regulatory subject are also welcome. Articles must be submitted at least 8 weeks prior to publication date. If you are unsure whether an article on your area of expertise would be of interest, or you would like a copy of our Author Guidelines, contact the Managing Editor at benedict.lam@topra.org to discuss your proposals. Please note that all articles are subject to peer review. For display advertising opportunities contact erik@topra.org.

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ABOUT THE COVER

The outline of a map of North America with its embedded medicinal products symbolises the region's healthcare regulatory landscape.

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Winning the regulatory race against time

BY **NANCY PIRE-SMERKANICH**, *Assistant Professor, Department of Regulatory & Quality Sciences, University of Southern California School of Pharmacy, US, and*
JULIE WARNER, *Vice President, Regulatory Affairs, Alan Boyd Consultants Ltd, UK*

Our world and the discipline of regulatory science is constantly changing. Never has this been more apparent than as we face this global pandemic and the regulatory response to it. While we would normally aim to offer a significant commentary on regulatory hot topics within our editorial, at the moment we are all very much aware of the challenge facing the global population in the current COVID-19 pandemic, and so many regulatory affairs professionals are fighting to keep on top of an ever-increasing workload to advance effective and safe products as quickly as possible.

Therefore, instead of telling you what you already know, it's worthwhile taking a few moments here to share some of the US resources that may be helpful. Firstly, the US FDA has created a useful landing page for the Coronavirus Treatment Acceleration Program,¹ which includes FDA blogs, what products are in development, how many trials the FDA has reviewed, what emergency use authorisations (EUAs) have been granted and links to resources for researchers and companies, along with information on the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, a critical initiative being coordinated by the Foundation for the National Institutes of Health (FNIH) with industry and government collaborators.

Two additional, and perhaps less well known, general resources are the Small Business Assistance webpage² from which you can access sites for drugs, devices and other centres and regional offices. Although intended for regulated small businesses, the Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) and the Division of Industry and Consumer Education (DICE) in the Center for Devices and Radiological Health (CDRH) are particularly helpful. The SBIA webpage³ has a list of (free) events and a dropdown menu that covers a myriad of topics. You can also navigate from there to the Regulatory Education for Industry (REDI) conferences and webinars, all of which have downloadable slides and presentations. The DICE site⁴ has links to "Device Advice" and is home to CDRH Learn, which is similar in design and content to the SBIA.

As a backdrop, let's not forget that the FDA is already undergoing a significant modernisation activity, as we see in an article summarising the steps the agency is taking to move towards more integrated, effective and

patient-focused reviews and approvals. It's often said that necessity is the mother of invention, so it will be interesting to see whether the current pandemic accelerates the development and roll-out of some of these new approaches to working. This theme runs in to our focus interview with two Director Generals at Health Canada on the activities undertaken by the agency to ensure it is ready for new technologies and platforms, such as

cell and gene therapies via its regulatory renewal initiative, the Agile Regulations Project. With such product types often including many novel aspects that don't always sit clearly in one category or another (eg, novel device, unique handling aspects), it's refreshing to see close collaboration within the agency in this regard. Finally, we highlight the recognised need for cooperation at both the regional and global level for combination products in a report on the TOPRA-RAPS joint workshop, which efficiently summarises the different stance of the FDA versus that of the European Commission and European Medicines Agency.

Moving away from our US focus, we are also fortunate to have two valuable updates, firstly on the status of the medical devices standards, which includes the March 2020 EU harmonised standards. The second includes a "one-stop" source of information on early access programmes in the EU in a handy tabular format, as a follow-up to an article in September 2020. Finally, we have a thought-provoking read on the challenges faced in the development of a semi-automated tool for text mining for document curation and automatic regulatory submissions in the context of the identification of medicinal products (IDMP) standards.

We would like to close out this editorial by encouraging everyone to maintain their reading and training during this difficult time (to perhaps avoid receiving penalties for non-compliance with FDA regulations, as highlighted in an article in this issue with regard to the clinicaltrials.gov database). ■

References

1. www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap
2. www.fda.gov/industry/small-business-assistance
3. www.fda.gov/drugs/development-approval-process-drugs/cder-small-business-industry-assistance-sbia
4. www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice



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**Regulatory affairs
 professionals are fighting
 to keep on top of an
 ever-increasing workload
 to advance effective and
 safe products as quickly
 as possible**”

INTERVIEW

In an exclusive interview with *Regulatory Rapporteur*, **CELIA LOURENCO**, *Director General, Biologic and Radiopharmaceutical Drugs Directorate*, and **DR J PATRICK STEWART**, *Director General, Therapeutic Products Directorate*, both at Health Canada, talk about how the agency ensures the safety of pharmaceutical and health products



Regulating healthcare products in Canada

BY AMAN KHERA,

Global Head of Regulatory Strategy, Worldwide Clinical Trials

Q: Could you tell our readers a bit about your background, what attracted you to the regulatory arena, and how you came to join Health Canada?

Celia Lourenco (CL): I completed a PhD in pharmacology and always had an interest in the area of drug development, and joined a lab doing my PhD studies that was involved in developing radioactive molecules. That really drove me into the area of drug development. At one point I noticed there was a post-doctoral fellowship opportunity at Health Canada, and I decided to apply, and the rest is history.

J. Patrick Stewart (JPS): I also started out with a science background. My initial training was in geology, I did a

geochemistry degree and then did a master's degree at University of Toronto in geology. Around the time I finished my master's degree, I was working in base metal exploration and the world base metal crisis resulted in a downturn, so employment opportunities weren't good, so I went back to school and did a medical degree. Subsequent to that, I did a residency in family medicine and emergency medicine and worked for 14 years in a tertiary care hospital, an emergency department in Ottawa. I spoke to a colleague who had moved over to Health Canada, and found it interesting, so I explored that opportunity and was hired as a medical officer in the Medical Devices Bureau 15 years ago.

Q: What does your current role involve, and what do you consider your favourite aspects of this role?

CL: I'm the Director General of the Biologic and Radiopharmaceutical Drugs Directorate, responsible for reviewing both clinical trials and authorising clinical trials, as well as market approval for biologics and radiopharmaceuticals, so I have a lot of responsibility. I get to work with incredibly smart people, scientists and experts, which is very intellectually stimulating. We're always learning about new therapies, and the science of drug development continues to change. I really enjoy contributing to ensuring Canadians receive drugs that are safe, effective and of high quality. I enjoy working with a variety of stakeholders, so not just my colleagues like Pat within the branch, but outside with a number of different stakeholders, within the government and outside the government, across all the sectors, including the healthcare system partners and industry stakeholders. We're all in this together with the ultimate goal of safe and effective drugs for Canadians.

JPS: I'm the Director General of the Therapeutic Products Directorate (TPD). It's one of the directorates in the health product and food branch, and we are responsible for prescription drugs and regulating drugs for human use. Before authorising the drugs, we verify that they meet safety, efficacy and quality requirements of the Food and Drug Act. We also approve clinical trials for therapeutic pharmaceuticals and look after the special access programme. I am part of a team of about 450 people, and I feel privileged to be in the role I am in and work with great colleagues like Celia at the branch level of the executive committee. It's an interesting job that is never dull. There are always new aspects and challenges. We're always looking for ways to become more helpful and stay relevant. What I find the most interesting is how things evolve and how we actually play a vital role, but we need to stay flexible at the same time, too, to stay relevant.

Q: What changes have you introduced within Health Canada at your directorates since you took on the role, and what are your aims for future changes within the organisation?

CL: I joined the directorate almost two years ago. I found it to be a solid, well-established and well-run organisation. It has met all its performance standards for what we call cost-recovered submissions, as well as non-cost-recovered submissions (ie, those for which industry pays fees versus those that it doesn't). We really have a fantastic team that is dedicated and ensures that we meet those performance standards, and makes sure we get drugs reviewed and approved on time. I did implement some realignments and a name change of the directorate, just to make it more precise about the products that we regulate, but the major functions of the directorate have been maintained. I do expect the directorate to evolve in the future as we expect new cutting-edge therapies to emerge, such as gene and cell therapy. That will certainly challenge us to adapt and be agile in how we will regulate in the future. I'm looking forward to that challenge.

JPS: Similar to Celia, the directorate I work in is staffed by an enormous amount of qualified, dedicated people, and, if I was to say I introduced any change within Health Canada, it's only to say that I contributed to the change because everybody is rowing in the same direction and we're working together. In the role of



Just before the COVID-19 pandemic, we were moving into a regulatory modernisation project that the whole branch was embraced in and we've been driving some of those projects out of the Therapeutic Products Directorate

Director General, you do have the ability to influence the focus, scope and effectiveness of these projects. I grew up in the TPD, the Medical Devices Bureau was there and I was leading the Office of Clinical Trials for a period; I was supporting the Director General and Director General's Office for a while, and I had a stint being the Director General of the Marketed Health Products Directorate (MHPD) and then, for the past three years, I've been back leading the TPD.

I've been involved in modernisation projects for the review of drugs and devices. TPD was leading seven of the 15 projects and I played a role in making sure that those advanced and had appropriate focus and were delivered. Just before the COVID-19 pandemic, we were moving into a regulatory modernisation project that the whole branch was embraced in and we've been driving some of those projects out of the TPD. I've been contributing to those projects. We as a branch also have focused a lot on our stakeholders, both within the department, as well as within the healthcare system, and also internationally.

I've had an opportunity to be involved in international organisations and built relationships and we are continuing to build stronger relationships. We also have an increasingly intertwined relationship with the European Medicines Agency (EMA) and of course the US FDA is always an organisation that we enjoy dialogue with. Going into the future, I hope that the TPD and our branch can continue to evolve. Regulatory change is not a quick process, it requires proper procedure and protocol and we try to think ahead of the game so that we can put in place changes that will support the evolution of how drugs are being developed, how the industry is functioning, and how the healthcare systems are evolving.

Q: Do you think Health Canada has been affected by the increasing requirement for global transparency in regulatory processes?

CL: Transparency has been one of our strategic priorities over the past several years. It did require a culture change. A decade ago, perhaps, we were "closed" by default, meaning that everything was confidential. Now transparency is the default in everything we do. We have implemented several transparency measures over the past several years. We have several initiatives, like our summary basis of decision document, which summarises the regulatory decision when a new drug is approved. We have shortened versions which we call regulatory decision summaries,

which provide a quick two-page summary of the decision on a drug approval, whether it's a new drug or a change to an existing drug.

We also have numerous databases. We have a clinical trials database that lists all clinical trials we have authorised. We have a drug product database that lists information about the products we have authorised in terms of the instructions for use and side effects associated with the drug. In April last year we launched the "Public Release of Clinical Information" initiative, which aims to provide information to healthcare providers as well as scientists, academics, and Canadians in general about the clinical safety and efficacy data that were used in the decision process, ie, the results of the clinical trials that were conducted to support the approval of the drug.

JPS: One other aspect is in the post-market space. We do a lot of safety reviews of drugs, and then may make decisions to change labelling or not. Up until about eight years ago we weren't very transparent about that, but we now also put out summary safety reviews that explain the process and rationale for our decisions and conclusions. If requested and required, we could also release the full review report.

The other thing we've evolved is our product monograph, the document that explains the information that was submitted about the product, the prescribing information and we've evolved the part 3 of that, which is for patients. We're trying to adapt that into more of an electronic format; our long-term vision is to have this available to pharmacists so they can easily access Canadian-specific information for patients about a product. We would also like Canadians to have access to our health product registry. We're trying to produce as much of the information available about the products we regulate in a user-friendly format and trying to make the language plain and understandable.

“ We've been able to continue to meet the performance standards despite the COVID-19 pandemic and have been expediting all of our COVID-19 clinical trials

Q: What is the average length of time it takes Health Canada to assess and approve applications, variations and renewals? What is the percentage of approvals being achieved within a timeframe?

JPS: We publish our annual report (available on our website) and the Centre for Innovation Regulatory Science (CIRS) produces a comparative report of different regulators. We have our various targets, we have priority review, expedited review, and standard review. We have our performance targets for our clinical trial applications and we have performance commitments. We have just introduced a new framework for cost recovery where we've had to meet our average performance time. Up until this year for every submission that we go beyond the cost recovery

performance target, there is a penalty applied, so our challenge is to try to approve every submission and make a regulatory decision within the cost recovery target. So far we're meeting our cost recovery targets. There's been a global shift to an increasing number of submissions being done as either priority or an expedited review. The FDA is leading that with the number of submissions in the past couple of years that follow expedited timelines.

With COVID-19-related clinical trial submissions, our default time is 30 days. We've been able to assess all COVID-19 trials in a much shorter time, some initially within a day or two. We've had one COVID-19 related drug submission, for remdesivir, and again, we were able to achieve the review in a six-week timeframe instead of the 180- or 220-day performance target.

Q: Do you have any generic substitution or reference pricing?

CL: From the biosimilars perspective, the pathway for market access is different from generics. It's not the same abbreviated new drug submission pathway but a regular new drug submission, with the data comparing the biosimilar to the innovator. We don't issue a declaration of bioequivalence. We review the application and issue an authorisation based on the data submitted and the drug then enters the market as a biosimilar. It's then up to the provinces to determine whether it is interchangeable or not, or whether it can be substituted. From our perspective, the review process confirms that we do not expect any meaningful clinical differences on efficacy and safety between the biosimilar and its comparator.

JPS: Under the Food and Drug Act, we do have an abbreviated new drug submission pathway where generic companies using bioequivalence studies on the Canadian reference product obtain a drug approval as an equivalent to an innovator product. They're then able to go to the various purchasing organisations within the provinces to get a declaration of equivalence and get generic substitution. All of the dealings beyond issuing an approval based on an assessment of the evidence provided, the pricing, whether it's deemed to be equivalent and the timelines of all that are done by the provincial bodies.

Q: Does Health Canada conduct health technology assessments or is there a separate body that carries out the economic assessment of medicinal products?

JPS: Yes, there are separate health technology assessment (HTA) bodies: the Canadian Agency for Drugs and Technologies in Health (CADTH) and INESSS (Institut national d'excellence en santé et services sociaux). The CADTH undertakes the HTA for drugs and some devices for all the provinces except Quebec, and INESSS undertakes it for Quebec.

Previously, for a drug or device submission, once the review of the safety, quality, and efficacy was completed, the notice of compliance (NOC) would be issued and then an HTA would begin. We started an initiative working with the CADTH and INESSS to move that up so that the HTA would start six months before a NOC issuance was suspected. We were able to develop that process, it was piloted and now, somewhere around 50% of the innovator submissions that are coming in the past year have taken advantage of this alignment process. One other aspect of that project was to try to put in place a joint early advice – ie, the HTA body and Health Canada would provide sponsors with earlier advice in the drug development planning. This will help sponsors

Regulation during COVID-19

Has the COVID-19 pandemic had any impact on your agency's operational activities?

CL: Definitely there have been impacts. Essentially most of my staff and my directorate of about 370 employees are working from home. I do have some staff working in the laboratories – those who are responsible for our lot release testing for biologics such as vaccines and staff in our laboratory research programme. But most of the other staff are working from home. We have some staff who are parents of small children and it has been challenging for them, but they have been able to adapt and continue to contribute to their role, which is incredible. We've been able to continue to meet the performance standards despite the COVID-19 pandemic and have been expediting all of our COVID-19 clinical trials. We've been able to continue to review the other regular clinical trials as well as drug submissions. We continue to hold meetings with sponsors and provide advice to stakeholders, but that's all shifted to virtual meetings. For the most part it's worked well, sometimes there are connection issues, but we've been able to work through

those. We're currently focused on ensuring we support the country's response to the pandemic from a regulatory perspective. We have taken measures to implement flexibilities, to facilitate clinical trials and to support our stakeholders at this unprecedented time.

JPS: It was a huge shift that we did quickly and successfully from working in the office to working at home. Some IT challenges were sorted out quickly. There was some flexibility afforded around hours of work and so forth and our staff are very resilient. Despite all these challenges we've been able to maintain our regular cost recovery performance targets, as well as expedite clinical trial reviews, as Celia has mentioned.

We've also been engaging more with other areas of the department and the government; other departments because of the need to call on expertise, and across the government because we needed to understand each other, how industry, science and economic development worked, how the public health agency was working, how we were working, and how our regulatory operation and enforcement

branch was working.

We've been involved in a lot more meetings where we're sharing our expertise and coming to share information on some of the decisions we've had to make. As Celia mentioned, we've offered regulatory flexibilities and put in place interim orders for the medical device authorisations. There was a lot of flexibility around hand sanitisers. We've put in place a clinical trial interim order and the regulatory operations enforcement branch put in interim orders around flexibilities with drug shortages. We have to look at the potential products coming in from a quality point of view have been supporting the regulatory operations branch. We continue to look at ways that we might advance other interim options to help.

Also, there has been a fair bit of engagement with the International Coalition of Medicines Regulatory Authorities, watching the COVID-19 clinical trials that are ongoing and trying to share as quickly as possible any results that are coming up. We've leveraged our relationships globally to commit to share information between regulators.

have a better sense of what the regulator and what the HTA assessor are looking for from endpoints to support decisions.

It is important to note that the agencies do work independently. Both the CADTH and INESSS have some similarities but their decisions are independent. Of course, their decisions are independent from Health Canada's decision. Health Canada is about the benefit–risk of a drug, whereas the health technology agencies look at cost–benefit.

Q: What is Health Canada's strategy to combat the distribution of falsified, counterfeit medicines?

JPS: It is a very challenging area. There are two aspects to this. You've mentioned falsified and counterfeit medicine. There's also falsified or misleading advertising around products. In our branch the Marketed Health Products Directorate (MHPD), in collaboration with the regulatory operation and enforcement branch, do have a programme to monitor advertising and promotion. There are clear statutes in our regulations around what can be said or not said about health products and their claims. This is monitored and they deal with misleading advertising. In the context of COVID-19, they've been more proactive in looking at unfounded claims and taking action. Regarding actual importation and distribution, there is a joint monitoring programme with the Canadian Border Services.

Q: What are some important updates to Health Canada legislation readers should be aware of?

CL: We implemented legislation last year to embark on a regulatory renewal initiative, which we refer to as our Agile Regulations Project. The intent is to renew the current framework

to eliminate outdated regulations and make it more risk-based and agile to respond to emerging technologies. We will be consulting with stakeholders in the coming months to move the project forward.

As part of that initiative we're also implementing a new advanced therapeutic products pathway, which will introduce a tailored approach to regulating innovative products that don't fit within the current regulatory framework. An example may be products such as 3D bio-printed tissues and 3D bio-printing of organs. Those may have characteristics that would fit, for example, our biologics framework, and other characteristics that would better fit under our medical devices framework. The objective is to tailor the requirements to ensure that the safety, efficacy, and quality of those innovative products will be appropriately managed and appropriately regulated. We will learn from the process and eventually determine whether such products can be transitioned into an existing regulatory pathway or a new pathway in the future. Products could also exit the market altogether if there are safety, quality or efficacy concerns.

We're also developing this particular advanced therapeutic products pathway to address those emerging challenging but interesting products, including gene therapies or cell therapy products that are individualised.

Q: How does Health Canada work with the EMA and the FDA?

CL: We work with the EMA and FDA on a multi-lateral level, such as through the International Coalition of Medicines Regulatory Authorities (ICMRA), International Council for Harmonisation, International Pharmaceutical Regulators Program and the



For a biosimilar, it's up to the provinces to determine whether it is interchangeable or not. From our perspective, the review process confirms that we do not expect any meaningful clinical differences on efficacy and safety between the biosimilar and its comparator

Pharmaceutical Inspection Co-operation Scheme. Those are also opportunities for us to engage with the EMA and FDA experts to share information and knowledge. We've actively engaged with these agencies on COVID-19 as well for the past several months, both within the context of ICMRA as well as outside of that forum. Exchanging information with them has really been helpful, such as approaches to vaccines for COVID-19. These are key relationships and we nurture and value them.

JPS: We value both these relationships strongly. We have reached out and engaged at many levels, both from the heads of agency down to operational levels and we find these relationships valuable. With the EMA, we have been permitted to participate in some of its committees and we engage in cluster meetings. All these various touchpoints are extremely valuable for us to discuss common files and aligning to a possible degree. We have established confidential agreements that enable us to share information which otherwise couldn't be shared.

Q: What have been your agency's successes to date and what have you been most proud of?

CL: We're proud of our quality management systems. We're ISO-certified, both in our regular operation as well as our laboratories. We also pride ourselves in conducting reviews with scientific rigour and discipline, ensuring that only products that meet those internationally recognised standards will enter the Canadian market.

JPS: I'm proud of our reputation globally. We're not the size of, say, the FDA, but we're at the table with leading global regulators like the FDA, the EMA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). Our teams and specialists are sought for input and we influence global decision making so, from the point of view of Canadians, they can have confidence that the skill sets and the type of work we're doing is aligned with what other major regulators are doing.

Q: What do you anticipate being the highlights of Health Canada during the next 12 months? What do you think will be the most important issues the agency will face in the future?

CL: We hope that over the next 12 months we can make very significant progress in bringing high quality and effective products to market to address COVID-19 because this pandemic isn't going away any time soon. We also plan to move forward

with the agile regulations and the advanced therapeutic products project. We also want to continue to engage internationally with our international partners through our Australia, Canada, Singapore, and Switzerland (ACSS) consortium. We want to evolve the work-sharing activities. It's very active and successful and we expect it to become part of normal business. We also want to continue to collaborate with other partners like the FDA, with which we are conducting parallel reviews in the oncology space.

JPS: We'll continue to evaluate non-COVID-19 therapeutics. There's still a vast number of clinical trials, special access programme requests and market authorisation requests coming in. We'll continue to strive to maintain our high standards for review of these and meet our performance targets.

Q: What do you see as the biggest challenge facing Health Canada in the next five years? What are your key objectives?

JPS: There are many challenges, but if I had to pick out a few it'd be the pace of change in scientific development, in manufacturing, and the design and modelling of trials. There is the evolution of what endpoints are relevant to Canadians with the use of real-world evidence and artificial intelligence modelling and to follow the changes in healthcare.

Globalisation is another big one, I think the drug shortage issues that have been happening over the past few years are partly because of globalisation and the lack of redundancy in the supply chain, but also globalisation in research and development. It's a competitive market to entice clinical trials and research and development in any domestic market based on global decisions around whatever factors they're considering. Because of all these factors we need to keep adapting our regulations to serve Canadians well, and to keep Canada on the radar as a country where global companies want to do research and development and where companies want to market their products. It is a competitive world out there and Canada only represents about 2% of the global sales market. We find that challenge is – in order to be able to be relevant and to be an effective regulator – we need to have the right skill sets. To evaluate these novel therapies to leverage advances in, for example, analytics and modelling, we may have to change some of the skill sets we are hiring for, so that we have people with slightly different backgrounds. And to adjust to these challenges and to stay relevant, we need to continue to enhance our international collaboration and work-sharing initiatives.

CL: In order for us to remain relevant as a regulatory agency and be able to be agile and respond quickly to innovative technologies as they evolve, we need to engage much more with the healthcare system, and with the innovators themselves to understand the technologies and to make sure we develop the right regulatory requirements that don't stifle innovation. And then, a follow-through right from the regulatory process all the way down to when the patient receives the treatment.

Added to that as well is the patient voice. Until recently, we have not necessarily engaged patients systematically such as how the FDA does. We need more patient engagement feeding into our regulatory processes and decision-making on challenging areas of regulation like orphan drugs and personalised medicines that may come through the advanced therapeutics pathway. ■

FEATURE

FDA issues guidance for 2017 final rule on penalties related to Clinicaltrials.gov database

We look at the final version of the FDA guidance that examines the powers the agency has to fine sponsors for failing to submit clinical trial information or results

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KEYWORDS

*FDA; United States;
Clinical trials; Data
governance.*

In August 2020 the US FDA published the final version of “Guidance for responsible parties, submitters of certain applications and submissions to FDA, and FDA staff”, which addresses how civil money penalties under the Federal Food, Drug, and Cosmetic Act [FD&C Act Section 303(f)] can be assessed.¹ That section of the law authorises the FDA to fine the sponsors of drug, biologic and devices applications for not submitting clinical trial registration and/or results information to the ClinicalTrials.gov data bank and the accompanying certifications to the FDA.

The guidance was issued to answer many of the questions that were not part of either the Food and Drug Administration Amendments Act of 2007, also known as FDAAA 801, which established the registry to promote transparency of clinical research to trial participants and the public, and what was included in the Final Rule of 2017 (42 CFR Part 11), which expanded the requirements for registering clinical trials and submitting results information. The FDAAA 801 requires that additional information be submitted to the clinical trials data bank (www.ClinicalTrials.gov) previously established by the National Institutes of Health and the National

Library of Medicine (NIH/NLM), including expanded information on which clinical trials were applicable and information regarding the results of clinical trials. The Final Rule clarified the requirement for sponsors to report the results from applicable clinical trials directly into ClinicalTrials.gov within one year of completion, and added requirements for reporting detailed adverse event information and inclusion of the full trial protocol and statistical analysis plan in the trial registry at the time of results reporting.

The terms “submitter” and “responsible party”, which are used in the Final Rule and new guidance, extend the responsibility for result posting to an individual or entity required to submit clinical trial information for an applicable clinical trial, and recognises that the submitter may be someone other than the responsible party. The Final Rule specifies that there must be one (and only one) responsible party for the purpose of submitting information about an applicable clinical trial. The sponsor of an applicable clinical trial will be considered the responsible party, unless and until the sponsor designates a qualified principal investigator as the responsible party.

The certification is the Form FDA 3674,



TABLE 1

Major Q&As addressed in “Guidance for responsible parties, submitters of certain applications and submissions to FDA, and FDA staff”

Question	Answer
How to identify violators?	Bioresearch Monitoring Program (BIMO) findings and complaints.
What will be the procedure?	Preliminary notice of noncompliance (Pre-notice letter), to include: <ul style="list-style-type: none"> ● Description of potential violation ● Requests that the responsible party takes any necessary actions to address the potential violation within 30 calendar days after receiving the letter.
Where will the Centers focus these efforts?	On those applicable clinical trials of products that potentially may pose a higher risk to human subjects or applicable clinical trials of products intended to address significant public health need. <ul style="list-style-type: none"> ● Products that have not previously been approved, licensed, or cleared by the FDA and are intended to treat serious and/or life-threatening diseases or conditions and applicable clinical trials involving vulnerable populations (such as paediatrics), rare diseases, or emergency research conducted without informed consent. ● Responsible parties or submitters who have had a pattern of previous noncompliance with the requirements to submit clinical trial information and/or certifications ● BIMO findings on noncompliance with other statutory and/or regulatory requirements pertaining to the conduct of the trial.
What are the procedures when the Center seeks civil money penalties?	FDA regulations governing civil money penalty proceedings are detailed in 21 CFR part 17. <ul style="list-style-type: none"> ● The Center with principal jurisdiction over the matter involved files a complaint ● The complaint will be signed by the FDA Office of Chief Counsel attorney for the Center and will prosecute violations, determine who is responsible and the amount of penalties and assessments the Center is seeking ● The complaint will include instructions for filing an answer to request a hearing and will warn that failure to file an answer within 30 days of service of the complaint will result in the imposition of the proposed amount of penalties and assessments.
What does the responsible party/submitter do?	Pays the penalty sought in the complaint or files their answer and contests the allegations. Legal proceedings follow.
How much are the penalties?	The maximum penalties are not more than \$10,000 for all violations, which are part of a single complaint but if not corrected within 30 days, an additional civil money penalty of not more than \$10,000 for each day that the violation continues after such period until the violation is corrected.
Any exceptions?	Yes – based on the nature, circumstances, extent, and gravity of the violation(s) and the ability to pay and stay in business, as well as any history of prior such violations and the degree of culpability.

The Centers will focus their efforts on those applicable clinical trials of products that potentially may pose a higher risk to human subjects or products intended to address significant public health needs

which must accompany applications that contain clinical study information for drugs and biologics, such as investigational new drug (IND) applications, new drug applications (NDA), biologics license applications (BLA), abbreviated new drug applications (ANDA) and any efficacy supplements to these applications; as well as medical device submissions requiring premarket approval applications (PMA), humanitarian

device exemptions (HDE), and 510(k) submissions that refer to, relate to, or include information on a clinical trial.

Violation and penalties

In this guidance, the FDA explains how the “Centers” (Center for Drug Evaluation and Research – CDER, Center for Biologics Evaluation and Research – CBER, and the Center for Devices and Radiologic Health – CDRH) intend to identify whether responsible parties have failed to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank or submitted false or misleading information to the data bank, or whether submitters have failed to provide the certification (Form FDA 3674) that is required. In addition, it addresses under what

circumstances may a Center decide to seek civil money penalties against a responsible party/submitter; what the procedure will be when a Center seeks civil money penalties; and what civil money penalty amounts may be assessed. The FDA intends to rely heavily on the Bioresearch Monitoring Program (BIMO) and a risk-based approach to which studies and product types they will focus on. Table 1 (see previous page) outlines the major questions and answers which are addressed in the guidance.

Impact

With the issuance of this guidance it is important to look at which organisations would be most impacted by FDA enforcement. In a February 2020 study published in *The Lancet*, researchers performed a cross-sectional analysis from data downloaded and extracted from ClinicalTrials.gov over an 18-month period (March 2018–September 2019), which showed that overall compliance with FDAAA 801 was poor.² Their analysis showed that industry was significantly more compliant than non-industry, and non-(US) government sponsors, and that sponsors running large numbers of trials were more compliant than smaller sponsors.

UK researchers from The DataLab at the University of Oxford included in their analyses all applicable trials due to report results under FDAAA, the first trials of which would have been due in January 2019. They also excluded trials that would not have a due date in that time period and those that would have received a deferral allowing for delayed reporting. Deferrals can be granted for studies, which are part of NDAs or investigational drug exemptions (IDE) at the request of sponsors based on “commercial confidentiality”.

In addition to the clinical study results which were submitted and publicly available on the FDA website, the authors were able to include those under quality control review by the CT.gov staff. Trials were classified as compliant if the results were submitted within one year of the primary completion date, as required by the legislation. Of the 4,209 trials that should have had results posted within the one-year timeframe, 40.9% did so, with 63.8% submitting results at some point beyond one year. Interestingly the average amount of time to post results was 424 days, or 59 days greater than the requirement.

The 2020 results demonstrate an improvement in complying with FDAAA 801 and they are consistent with other analyses of compliance with not only the US but other global registries. In an earlier study, published

before the 2017 Final Rule that looked at the US database, only 13.4% of trials reported summary results within 12 months after trial completion, whereas 38.3% reported results at any time up to 27 September 2013.³ A similar type of study was conducted on the EU Clinical Trials Register (EUCTR) to measure compliance with posting results to the registry within 12 months of completion.⁴ This analysis showed that half of all trials were non-compliant and, like *The Lancet* study, trials with a commercial sponsor were substantially more likely to post results than those with a non-commercial sponsor.

In *The Lancet*, it was noted that industry sponsors are about three times more likely to be compliant with the trial results reporting legislation than academic sponsors. Of the 13 sponsors with more than 30 trials due to report results, six were drug manufacturers that had compliance rates between 93% and 100%. They also provided data on seven major university medical centres in the US that had compliance rates between 16% and 92%.⁵

These authors concluded that lack of compliance with FDAAA 801 was mainly due to lack of enforcement by regulators. They also highlighted the need for effective action, including enforcement from sponsors, and called for public audit of compliance for individual sponsors using open source data and tools.

The detailed information on enforcement and the procedure for assessing civil money penalties has been the subject of much study and discussion. More than one research team has estimated that if the FDA strictly enforced the actions in the Final Rule, millions or even billions of dollars in fines could have been collected.^{2,5} No such fines have been imposed by the FDA to date but with the issuance of this guidance it will be interesting to see if that will change. ■

References

1. FDA. Guidance for responsible parties, submitters of certain applications and submissions to FDA, and FDA Staff, August 2020. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/civil-money-penalties-relating-clinicaltrialsgov-data-bank> (accessed 14 September 2020).
2. DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *The Lancet* (British edition). 2020;395(10221):361–369. doi:10.1016/S0140-6736(19)33220-9
3. Anderson ML, Chiswell K, Peterson ED et al. Compliance with results reporting at ClinicalTrials.gov. *The New England Journal of Medicine*. 2015;372(11):1031–1039. doi:10.1056/nejmsa1409364
4. Goldacre B, DeVito NJ, Heneghan C et al. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource. *BMJ* 2018;362:k3218–k3218. doi:10.1136/bmj.k3218
5. Erik von Elm, Joerg J Meerpohl. Trial results reporting: FDA Amendments Act Final Rule needs enforcement. *The Lancet* 2020;395(10221):316–317.

A study in *The Lancet* showed that industry was significantly more compliant than non-industry, and non-(US) government sponsors, and that sponsors running a large number of trials were more compliant than smaller sponsors

FEATURE

How the modernisation of FDA's New Drugs Regulatory Program enhances transparency

This article provides an overview of how the US FDA's New Drugs Regulatory Program identified opportunities and implemented new initiatives and the importance of these changes to the biopharmaceutical industry

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The US FDA's Center for Drug Evaluation and Research (CDER) is well recognised globally as a leader in the regulation of biopharmaceutical products.

Recognising the evolving science and technology, the CDER embarked on modernising its framework for the New Drugs Regulatory Program by implementing programmes to be more problem-focused, interdisciplinary, and team-based while incorporating the patient voice in development.

The CDER's mission is to protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients. The CDER achieves this mission for new drug products and original therapeutic biologics through the New Drugs Regulatory Program. The Office of New Drugs (OND) in the CDER has the primary responsibility for reviewing and approving new pharmaceutical products (drugs and biologics). The CDER reviews dossiers, ie, new drug applications (NDAs), Biologics License Applications (BLAs), and variations, ie, efficacy supplements, using cross-discipline teams, and this was more structured and consistent with the implementation of the Prescription Drug User Fee Act (PDFA) in 1992. Each discipline eg, medical, pharmacology/toxicology, clinical pharmacology, quality and often many other important disciplines, depending on the issue raised by the application, created their review independently. Although disciplines communicated and shared information with each other, there was a lot of duplication of work. A continued increase in review workload without corresponding increases in resources necessitated an emphasis

on making the day-to-day review process more efficient through process improvement and technology enablement.

Further, the development of biopharmaceutical products has become more complex due to advances in science and technology, eg, use of novel approaches and tools, and new technology is now available to facilitate development, review, and communication. These advances require review teams to develop their expertise to ensure these new advances are integrated into regulatory decision making. Pace, scope, and complexity of new innovations require deeper subject matter expertise, evolution of regulatory policy, and introduction of new analytical techniques. Although the New Drugs Regulatory Program has been successful in the past, the CDER recognised the need to improve its review framework.

New drug modernisation initiatives

In 2017, the OND embarked on a programme to modernise the regulatory review processes. The modernisation is a long-term process of continuous improvement involving multiple initiatives, from enhancing expertise and creating multidisciplinary teams to creating new knowledge management systems and reorganising review divisions.¹ The initiatives were grouped into six key strategic objectives, as outlined below.

Scientific leadership

The scientific leadership objective elevates the CDER's ambition around actively participating in shaping the drug development ecosystem for the benefit of public health. The main objective is to grow our scientific expertise, focusing on areas of unmet medical need, and to work to enhance development and provide greater clarity for developers on the pathways to regulatory approval in these areas. This strategic objective also focuses on innovations in trial design (eg, novel endpoints, new trial designs), evolution in regulatory policy and pathways to support paths to approval, encouraging developers to bring forward drug candidates in areas of need by providing new tools and regulatory clarity. With the changing drug development landscape, and the need

KEYWORDS

FDA; United States; Center for Drug Evaluation and Research.



The modernisation is a long-term process of continuous improvement involving multiple initiatives, from enhancing expertise and creating multidisciplinary teams to creating new knowledge management systems and reorganising review divisions

to focus on areas of unmet need, scientific leadership also means actively participating in exchanges with the broader scientific community reflected in presentations at scientific meetings and publications.

Integrated assessment

The integrated assessment strategic objective aims for a more consistent and efficient team-based, issue-focused assessment process and output, assuring robust debate and careful consideration of all individual viewpoints and perspectives to assess critically whether information in drug approval applications meets legal and regulatory requirements. The outcomes for this objective include

development of clear, thoroughly documented, and systematically communicated regulatory decisions, in addition to strengthened alignment or clearly articulated disagreements, across the cross-disciplinary team on the rationale underpinning approval decisions. This strategic objective includes building out operations that are more efficient and interdisciplinary in nature, earlier leadership engagement in review issue identification and resolution, and improved, issue-based, integrated communication to sponsors and external stakeholders. At the same time, the process embraces disagreement requiring frequent, issue-based discussions within and across disciplines intended to bring out and address areas of non-alignment,

seeking the best solutions to the issue, but also assuring that different viewpoints are heard and incorporated, and, if agreement is not achieved, clearly documented.

Benefit-risk monitoring

The benefit-risk monitoring strategic objective aims to enhance the CDER's ability to manage the benefit-risk profile of regulated therapies. This is achieved through strengthened approaches to identifying and managing risks across the lifecycle to monitor systematically the benefits and risks of drugs pre- and post- approval to protect the American public. This strategic objective aims to ensure a net positive impact on patient health by increasing the availability of timely, reliable benefit-risk information to inform treatment decisions and support safe use. The aim of this objective is to ensure efficient and effective multi-disciplinary collaboration on safety-related issues and enhance approaches to identification and management of potential risks/safety signals.

Managing talent

Maintaining a strong, energised workforce is central to maintaining a robust New Drugs Regulatory Program. Although hiring challenges have persisted over several years, the core challenge relates to more than just the quantity of colleagues working in the programme. There is an urgent imperative to not only hire additional staff, but also to develop colleagues, engage them in meaningful work, and consistently build new capabilities. The outcome the programme strives towards is simple: develop and maintain an exceptional reputation for recruiting, developing, and retaining top talent and scientific leaders. This strategic objective relates to successful recruitment of new talent from new sources, reducing unwanted attrition through improved incentives, development opportunities, and the creation of a stimulating scientific work environment.

Operational excellence

Despite the knowledge-intensive nature of the programme-related work, there is nonetheless a considerable amount of transactional work embedded in programme operations that benefits from disciplined management approaches and strong enabling technology. Optimising core regulatory workflow is critical to enabling other strategic objectives (eg, scientific leadership, talent management) because it creates time and space to invest in activity beyond day-to-day workload activity. Standardising workflow, business processes,

Understanding the changes in process and programmes early, especially those related to enhancing communications, should foster better collaboration during drug development and increase probability of success

roles, and responsibilities improves operational efficiency and enables our scientists to focus on science. The outcome is to have operations that lead to increased scientific leadership and prompt impactful internal advancement of public health. This objective also relates to reducing time on ancillary tasks outside specific roles and responsibilities to spend more time on value-adding activities and developing technology-enabled workflows.

Knowledge management

The programme review processes are data-rich and knowledge-intensive, with numerous data types and sources (both externally submitted and internally generated). To allow for efficient access and sharing of institutional knowledge and to aid in review activities, the CDER has undertaken several efforts to develop and enable infrastructure, capabilities and change management to better gather, organise, and disseminate its institutional knowledge for improved decision-making and accountability across its organisations. In the long term, the knowledge management strategic objective aims to create a culture of sharing and learning through increased transparency, data quality, and heightened collaboration with internal and external stakeholders. It also seeks to support business and programme innovation by consistently, repeatably, and continuously enabling improvements to regulatory processes and programmes. The strategic objective outcomes include greater capture and integration of knowledge across the programme, increased availability of business-relevant information and data to support regulatory decisions, and more consistent data capture through standardised processes and templated artifacts.

Workstreams

Guided by the strategic objectives described above, the following workstreams were formed to address the pain points:

- **Integrated review for drug marketing applications** Developing a streamlined interdisciplinary review process and template to support the new integrated review for assessing dossiers

- **Investigational new drug (IND) review management** Streamlining the IND scientific review processes for managing IND applications, beginning with 30-day safety reviews and protocols
- **Post-market safety management** Creating a more standardised and consistent approach to post-market drug safety
- **Assessing and developing talent** Developing a more effective and consistent process for hiring, onboarding, developing, and evaluating our scientific and regulatory review staff
- **Administrative operations** Optimising administrative and clerical staff roles, structure, and functions to enhance customer focus and employee engagement
- **Transition management and reorganisation of the new drug regulatory programme** Planning, coordinating, and implementing modernisation and organisational changes across the OND.

The reorganisation of the OND, approved in September 2019 by the US Congress, created offices that align interrelated disease areas and divisions with more disease-focused areas of expertise. The final step of the restructure was completed in April 2020. The changes increase the number of offices that oversee the review divisions from six to eight and increase the number of clinical divisions from 19 to 27, plus six pharmacology/toxicology review divisions. In addition to enabling greater efficiency, these changes are expected to help the OND better understand the diseases intended to be treated by the drugs it evaluates for approval—another way it aims to enhance its knowledge management and scientific leadership.

As each of these workstreams progressed, the CDER provided routine updates and solicited input from stakeholders to ensure transparency and mitigate any potential negative impact on drug development.

Industry's perceived impact of changes

Industry stakeholders recognise the significant changes that are occurring and understand

that it will take time to implement many of the changes. The OND's commitment in engaging stakeholders throughout the process has been key in ensuring transparency and gaining support. Understanding the changes in process and programmes early, especially those related to enhancing communications, should foster better collaboration during drug development and increase probability of success. The initiatives the CDER has embarked on to modernise the regulatory process should provide for better predictability, consistency, and transparency – all of which are important to successful and efficient drug development. The integrated assessment, along with the establishment of an Office of Policy within the OND, should enhance the ability to provide greater consistency by sharing information across review divisions and helping to increase knowledge and expertise across review divisions. The knowledge management system should also help to identify areas where additional guidance for industry is needed to create more efficiencies in development by reducing uncertainties. Aligning review divisions into more focused areas should help reviewers share information and allow for more consistent messaging to sponsors on similar issues. Additionally, as new innovative and complex therapies are developed, efforts to enhance scientific expertise and leadership at the OND should help to increase efficiencies and consistency in regulatory decision-making. The ongoing commitment to strive to enhance current programmes should continue to help deliver new therapies to patients in a more efficient manner.

Summary

With the fast evolving changes in science and technology, it is important for regulatory systems to adapt and create flexible, agile frameworks that still provide the same level of scrutiny in evaluating risks and benefits but in a more efficient manner. More importantly, it is also critical for regulators to engage with stakeholders as they make those changes to avoid any negative downstream impact on drug development and ensure patients will gain access to new therapies in a timely manner. All stakeholders should also understand that many of the changes require a change in culture and thinking and the full benefits may take some time to materialise. ■

References

1. Modernizing FDA's New Drugs Regulatory Program. 17 January 2020. Available at: www.fda.gov/drugs/regulatory-science-research-and-education/modernizing-fdas-new-drugs-regulatory-program (accessed July 2020).



ADOBE STOCK

MEETING REPORT

TOPRA/RAPS Workshop on Alignment of Global Combination Products

TOPRA and the Regulatory Affairs Professionals Society (RAPS) partnered for their second joint inter-regulatory and stakeholder workshop. This event looked at differing regional approaches to combination products and the potential for alignment of global regulations

REPORTED BY

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Introduction

The TOPRA/RAPS inter-regulatory and stakeholder two-day workshop held in June 2020 focused on global combination product regulations. The diverse panel of speakers included representatives from the European Medicines Agency (EMA), EU notified bodies, US FDA officials, regulators from Health Canada, the Malaysia Medical Devices Agency, Anvisa, the UK's Medicines and Healthcare products Regulatory Agency and industry experts, all exploring the challenges and looking for commonalities in the regulation of medical products with both drug and device components.

Brian Savoie, VP of Educational and Professional Development at RAPS and Samantha Cooper, Director of Professional Development at TOPRA, welcomed the attendees and presenters and opened the workshop with an innovative poll about

priorities. The focus of the workshop was to discuss different perspectives, share best practices, quality management and solutions for challenges for combination products.

Combination products, current approaches, challenges, insight & trends: The view from the US

Speaker: John Barlow Weiner, Associate Director for Policy Office of Combination Products, FDA

Combination products are common in everyday medical use, from a simple pre-filled syringe to a complex drug-eluting stent. From a regulatory perspective, however, they fall outside the traditional therapeutic and device pathways and provide unique challenges to both industry and regulatory authorities in ensuring their safety and effectiveness.

Clinical aspects, such as bridging studies and post-marketing requirements, combined with harmonisation are some of the highest pain points industry would like to see addressed

Most regulatory authorities have formal definitions in regulation, as well as a formal regulatory determination mechanism. However, no specific regulatory submission format exists for combination products. They must use existing drug, device, or biologic application/submission procedures, and, in some instances, multiple applications may be needed. The determination as to which regulations, submission procedure, and pathway to market is to be followed is based on the primary mode of action (PMOA), a risk-based approach that is defined by the FDA as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product”.

The FDA, which recognises combination products as a legally distinct entity, has very few regulations to guide an approval process. However, the FDA has an office dedicated to helping industry known as the Office of Combination Products. The review teams of the three FDA Centres (Center for Drug Evaluation and Research [CDER], Center for Biologics Evaluation and Research [CBER], and Center for Devices and Radiological Health [CDRH]), decide the appropriate pathway for a particular combination product through a determination mechanism called a Request for Designation (RFD) process. This process is designed to give manufacturers the opportunity to present their combination product, describe what they feel is the PMOA with evidence compiled to date, and receive a binding (or non-binding, in the case of a more informal pre-RFD) designation of lead FDA Center and regulatory pathway. The FDA is quick to point out that a combination product is distinct from a device, drug, or biologic. However, the RFD is where the uniqueness of being a combination product, in terms of regulation, stops as the submission format will follow that of the PMOA. If the PMOA cannot be determined or is equal among the components of the combination product, then the submission format of the FDA Center with the most relevant experience in similar combination products or closely matching safety and effectiveness questions is chosen. Unfortunately, unlike the Q-submission

programme which enables submitters to have early collaboration and discussions about medical device submissions, there is little opportunity for manufacturers to discuss their combination product during the RFD process except on very rare occasions. This, coupled with the difficulty for device companies to discuss drug delivery devices with the FDA without a therapeutic identified for use with the device beforehand, has severely limited innovation. It has led to development delays, as the need for a large pharma partner tends to be a significant hurdle for the smaller device companies.

EU Medical Device Regulation and In Vitro Diagnostics Regulation – Impact on the EMA

Speaker: Armin Ritzhaupt, European Medicines Agency

The EU does not specify a distinct term by regulation for combination products. The Medical Device Regulation (MDR) that supersedes the previous Medical Devices Directive (MDD) includes articles addressing devices designed and sold with a medicinal product as an integral part. These drug-device combinations are separated into the following categories: devices integrating a medicinal product, medicinal product integrating a device, and devices intended to administer a medicinal product when presented as a single, integrated unit, not reusable. In addition to defining the categories, Article 117 went on to modify Directive 2001/83/EC governing medicinal products for human use. The amendment essentially states that when the manufacturer of a drug-device combination product submits a marketing authorisation application (MAA) to the EMA, it must include an official certificate of conformity that shows that the device portion complies with the MDR. The literal reading of the EU regulation implies that approval is needed for each component of a combination product.

The EMA has attempted to clarify its position by publishing a guideline on quality requirements of medicinal products that

have a device component for delivery for use with the medicinal product. The clarification states that the notified body assessment and marketing authorisation review would not result in duplicate assessments. The notified body reviews the device alone, and the marketing authorisation review assesses the implications of drug-device product on the safety and efficacy of the drug product.

The FDA attempts to limit a combination product to a single marketing application to prevent duplication of work by a manufacturer, unlike what the EMA process requires in the case of companion diagnostics (CDx). The FDA is less rigid than the EU process, which requires both a device and drug or biologic submission for approval. Both submissions are approved at the same time resulting in one submission, usually the device, being held until the other is complete. In addition, although the guidance allows for all device submission types – 510(k), de novo, premarket approval (PMA) – to date, all but one CDx has required a PMA, suggesting that although two separate submissions are required, the risk level of both submissions is determined by the higher risk therapeutic.

As we observe an increased number of innovative combination products in the areas of drug delivery, artificial intelligence, and CDx, the limitations of the current regulatory pathways become more apparent. Regulatory authorities realise the need to be agile and creative in their thinking, but consensus on how to look at combination products differs dramatically based on whether it is viewed from a device or therapeutic perspective. Although PMOA determination is a common way to identify the appropriate regulatory pathway, it is limited and may contribute to “pigeonholing” combination products in one pathway or another. This works in most cases as the presence of a therapeutic usually is enough to guide the pathway. However, it quickly breaks down as device aspects become more complicated and play a larger role in the combination product. The risks associated with artificial intelligence systems and companion diagnostics becomes as much as, or more than, a therapeutic component. Coupled with the fact that industry is the technical expert for its own technology, and not the regulatory authorities, the result is complicated.

PMS/PMCF under the EU MDR for device-drug combination products

Speaker: Sophie Tabutin, WL Gore & Associates, France

From an industry perspective, there is justifiable frustration, but what about for patients?

Although long, and likely requiring some duplication of effort, the review process for combination products that make it to the market is thorough, in terms of safety and effectiveness. Treatment outcomes, in theory, are better for patients, with fewer adverse effects and increased efficacy. However, these new combination products will be much slower to arrive on the market. This greatly delays patient access to technologies with such benefits as decreasing the burden of taking medicines, releasing therapeutics at a regulated rate to increase efficacy, reducing the chance of overdosing or underdosing, and increasing compliance with drug regimens by making them simpler. This further illustrates that regulatory authorities need to take a closer look at how combination products are reviewed and ultimately reach the market. Improved outcomes and fewer adverse events are a distinct primary driver, but caution and careful thought must be considered to continue to ensure combination products are reviewed and determined to be safe and effective.

Challenges for global development and registration of novel and innovative combination products at a time of rapidly evolving regulations

Speaker: Daniela Drago, RAC Senior Director Regulatory Sciences, Biogen

How do regulatory authorities go about achieving effective regulation of combination products? Fortunately, industry and regulatory authorities can agree on the basis to reach this goal. Clinical aspects, such as bridging studies and post-marketing requirements, combined with harmonisation are some of the highest pain points industry would like to see addressed. Frequent and early communication increases harmonisation and avoids diverging opinions. Clinical studies designed for the combination product and not its constituent parts help prevent overly large studies. Post-marketing requirements specifically designed for combination products allow manufacturers

to adequately plan. These examples demonstrate that combination products should be independent of their constituent parts, not only in definition, but also in submission type and regulatory pathway.

QMS as a common global requirement: FDA guidance

Speaker: Kim Trautman, Executive Vice President, Medical Device International Services, National Science Foundation (NSF) International

Consensus standards offer an opportunity to come together and solve the problem. However, caution must be taken to avoid a dominant therapeutic or device viewpoint. A cross-cutting approach must be taken to bring the groups together, something which is difficult, as both the drug and device industry and drug and device regulatory pathways are radically different. A neutral party is sorely needed to step in and bring these thought processes together, but it is still unclear if the various standards organisations can do so. In addition, any standardised effort needs to reach all stakeholders. Current standardisation efforts tend to be exclusive to those that have the time and resources to participate in them. Although welcome to all, smaller device companies typically cannot afford to make their voices heard, despite being the very place where most innovation happens. Still, consensus standards do provide the framework where industry and regulatory authorities can come together and solve complex problems, as this process has been proven several times over.

Consistency and transparency with current processes is also key. Sharing of lessons learned can prevent the same hurdles from being resolved each time they arise. Unfortunately, issuance of formal guidance is slow. New recommendations have shown up in FDA submission reviews first, instead of in the draft guidance. This creates difficulties for manufacturers as it implies the landscape of the regulatory process may change part way through, something that can be costly

and, ultimately, detrimental. It also shows that conflict and differences of opinion exist within regulatory authorities. This, first and foremost, needs to be resolved. Using FDA as an example, the three Centres must be on the same page with combination products before progress can be made on harmonising the review process. The Office of Combination Products has made great strides in determining the designation of combination products, as well as helping industry identify a regulatory submission type, but perhaps it should have more internal authority to increase consistency and harmonisation of the three Centres.

Regulation of drug-device combination products in Canada

Speaker: Douglas Watson, Senior Policy Analyst, Health Canada

Pilot programmes and “sandbox” efforts may offer an opportunity for regulatory authorities and industry to collaborate on a review pathway unique to combination products. The Canadian combination product sandbox effort is an excellent example of this and shows promise in coming to a solution on combination product regulation. Pilot programmes in the areas of modelling, simulation, and software applications have been successful in the past with the FDA. Inviting industry to participate in parallel review programmes gives regulatory authorities the ability to test ideas without affecting existing processes. They provide direct application for review teams and allow the participation of both small and large industry to participate. This approach can be coupled with consensus standards efforts to offer insights across geographical regions.

Just like the very definition of the problem to be solved, a combination of the above methods, as well as industry and regulatory authority collaboration, provides a pathway to handle the uniqueness of combination products. The first step must be open communication. As demonstrated by the enthusiasm shown in recent years by regulators and the increase of combination product submissions by industry, it seems all stakeholders are fortunately willing to come together with this goal in sight.

Additional effort will be required to equal the rapid innovations in combination product technologies being developed today. Regulatory authorities and industry must come together to develop solutions through continued open dialogue, standards efforts, and innovative regulatory pathways. ■

The FDA attempts to limit a combination product to a single marketing application to prevent duplication of work by a manufacturer; it is less rigid than the EU process, which requires both a device and drug or biologic submission for approval

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Early access in the EU: a heterogeneous landscape with room for harmonisation

AUTHORS

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In the September 2020 issue of *Regulatory Rapporteur* we presented an analysis of early access programmes (EAPs) across the 27 EU members states plus the UK, suggesting a need for greater regulatory harmonisation in order to provide timely access to potentially lifesaving medicines. The table below summarises our findings in terms of not only availability, but also key administrative and operational requirements, of EAPs across Europe via compassionate use programmes (CUPs) and named patient programmes (NPPs). Data were compiled in Q1 2019 through

national competent authorities (NCAs) and/or ministries of health websites, literature review, and by online searches using country-specific search terms from the healthcare domain. NCAs were also directly contacted in instances when information was not readily available online. Our results reveal a largely heterogeneous landscape and point to important considerations for stakeholders considering implementing EAPs in Europe. More detailed discussion to accompany this table is available in our original article (*Regulatory Rapporteur*, Vol 17, No 9, September 2020, p28–32).

TABLE

Early access programmes overview across European member states

Country	Compassionate use programme (CUP)								Named patient programme (NPP)			
	Regulatory framework	Specifics	Maximum duration	Local representation	Timeline	Fees	Safety/PV reporting obligations defined?	Can the medicinal product be charged?	Regulatory framework	Timeline	Safety/PV reporting obligations defined?	Can the medicinal product be charged?
Austria	§8a, Austrian Medicinal Products Act, 2009	Results from Phase III trial should be available. CUP eligibility assessed on a case-by-case basis for medicinal products in Phase II studies.	Until commercially available	–	1–3 months	Yes	Yes	–	§8(1)2, Austrian Medicinal Products Act, 2009	–	Yes	Yes
Belgium	Art 106, Royal Decree of 14/12/2006 as amended by the Royal Decree of 25/04/2014	–	Until commercially available	Yes	60 days	Yes	Yes	Yes	Art 107/1, Royal Decree of 14/12/2006 as amended by the Royal Decree of 25/04/2014	–	–	No
Bulgaria	No provisions								Ordinance No 10 of 17/11/2011	7 days	Yes	–
Croatia	Art 3.72, Medicinal Products Act of 18/06/2013	–	–	–	–	–	–	–	No provisions			
Cyprus	No provisions								No provisions			
Czech Republic	Section 49, Act No 378/2007 of 06/12/2007 on pharmaceuticals	CUP is referred to as Specific Treatment (or Therapeutic) Programme (STP)	Until commercially available	–	–	Yes	Yes	Yes	Section 8, Act No 378/2007 of 06/12/2007 on pharmaceuticals	–	–	–
Denmark	Section 29, Part 1, Medicines Act of 16/01/2018	The national law covers both CUP and NPP under the same framework.	5 years	Yes	–	No	Yes	Yes	As per CUP	24hrs in urgent cases	Yes	Yes
Estonia	Medicinal Products Act of 16/12/2004	The national law covers both CUP and NPP under the same framework. Eligible medicinal products should have completed at least Phase II studies.	–	–	–	–	Yes	Yes	As per CUP	–	Yes	Yes
Finland	Medicines Decree 693/1987, 1184/2002 and 868/2005, and Section 21f Medicines Act 395/1987	Compassionate use is divided between access to a medicinal product for a group of patients in a hospital (CUP) or for individual named patients in ambulatory care (NPP).	1 year	–	30 days	Yes	–	–	As per CUP	30 days	–	Yes
France	Art L.5121–12 of the French Code of Public Health	CUP is referred to as cohort Temporary Authorisation for Use (cATU). In France, CUP data is assessed / reviewed by HTA bodies.	1 year ^(a)	Yes	–	No	Yes	Yes	As per CUP	–	Yes	Yes
Germany	Section 21(2) No 6 and Section 8o, German Medicinal Products Act	–	1 year ^(b)	Yes	14–60 days	No	Yes	No	Section 73(3), German Medicinal Products Act	–	–	Yes
Greece	Second issue, issue No 558, Government Gazette of the Hellenic Republic	The national law covers both CUP and NPP, referred to as EAPs, under the same framework.	1 year ^(b)	Yes	–	No	Yes	No	As per CUP	–	Yes	No
Hungary	No provisions								Section 25/C, Act XCV of 2005 on Medicinal Products for Human Use	3–21 days	Yes	No

(a) Can be renewed; (b) May be extended; “–” No data available at the time of query.
CHMP – Committee for Medicinal Products for Human Use; EMA – European Medicines Agency; HTA – Health technology assessment; MA – Marketing authorisation; PV – Pharmacovigilance.

TABLE (CONT.)

Early access programmes overview across European member states

Country	Compassionate use programme (CUP)								Named patient programme (NPP)			
	Regulatory framework	Specifics	Maximum duration	Local representation	Timeline	Fees	Safety/PV reporting obligations defined?	Can the medicinal product be charged?	Regulatory framework	Timeline	Safety/PV reporting obligations defined?	Can the medicinal product be charged?
Ireland	No provisions								Medicinal Products Regulations 2007 (SI No 540 of 2007) as amended	–	Yes	Yes
Italy	Decreto Ministeriale of 07/09/2017	The national law covers both CUP and NPP under the same framework. Eligible medicinal products must have ongoing/ completed Phase III studies or, in special cases, Phase II or Phase I. “Law 648” also permits the supply and reimbursement of products that do not have an MA, albeit under different conditions to CUP/NPP.	–	–	–	No	Yes	No	As per CUP	–	Yes	No
Latvia	Cabinet of Ministers Regulation No. 416 of 26/06/2007	The national law covers both CUP and NPP under the same framework.	–	–	–	–	Yes	No	As per CUP	–	Yes	No
Lithuania	No provisions								Order of the Minister of Health No V-374 of 09/05/2005	–	Yes	–
Luxembourg	A CUP framework exists but limited information available	–	–	Yes	–	–	–	–	An NPP framework exists but limited information available	–	–	–
Malta	A CUP framework exists but limited information available	Application are treated on a case-by-case basis.	–	–	–	–	–	–	Circular 270/06, Guidelines governing the use of medicinal products for human use without an MA, 2006	–	Yes	–
Netherlands	Art 40, section 3f, Dutch Medicines Act and Art 3.18 Ministerial Regulation	–	1 year ^(a)	–	–	–	Yes	No	Art 40, section 3c, Dutch Medicines Act and Art. 3.17 Ministerial Regulation	8 weeks	Yes	Yes
Poland	No provisions								No provisions			
Portugal	Deliberation No 80/CD/2017 of 24/10/2017	The national law covers both CUP and NPP, referred to as EAPs, under the same framework.	6 months ^(b)	Yes	5–15 days	No	Yes	No	As per CUP	5–15 days	Yes	No
Romania	Order No. 1018, Official Gazette of Romania No 663 of 09/09/2014	The law defines the categories of medicinal products that may be eligible for a CUP (eg, biotechnological product, orphan products and those targeting specific therapeutic areas).	6 months ^(a)	Yes	60 days	–	Yes	–	No provisions			
Slovakia	No provisions								No provisions			
Slovenia	Medicinal Products Act (ZZdr–2) 2014	The NCA shall obtain an opinion from the CHMP at EMA before making a decision on the application.	Until commercially available	Yes	7–30 days	No	Yes	No	Art 20, Paragraph 3, Medicinal Products Act (ZZdr-2) 2014	–	–	–
Spain	Real Decreto 1015/2009 of 19/06/2009	The national law covers both CUP and NPP under the same framework.	–	Yes	3 months	–	Yes	Yes	As per CUP	–	Yes	Yes
Sweden	Regulations LVFS 2008:1 and LVFS 2011:3 of the Medicines Products Agency	The national law covers both CUP and NPP under the same framework.	Until commercially available	–	60 days	No	Yes	No	As per CUP	–	Yes	–
UK	Human Medicines Regulation	CUP is referred to as Early Access to Medicines Scheme (EAMS). Primarily aimed at medicines that have completed Phase III trials but might be applied to completed Phase II trials. Access to the scheme requires prior promising innovative medicine (PIM) designation.	1 year ^(a)	No	75–90 days	Yes	Yes	No	Regulation 167, Human Medicines Regulation (SI 2012/1916)	28 days	Yes	Yes

(a) Can be renewed; (b) May be extended; “–” No data available at the time of query.
CHMP – Committee for Medicinal Products for Human Use; EMA – European Medicines Agency; HTA – Health technology assessment; MA – Marketing authorisation; PV – Pharmacovigilance.

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Text mining for regulatory intelligence: taking an automated approach

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KEYWORDS

IDMP; ISO; Text mining; Natural language processing; GxP; Computer system validation; Summary of product characteristics (SmPC); Regulatory intelligence.

ABSTRACT

In the healthcare domain, regulatory authorities worldwide have been taking stringent measures for data standardisation and harmonisation related to medicinal products. One recent example is the identification of medicinal products (IDMP), which is based on a set of five ISO norms adopted by the European Medicines Agency (EMA). IDMP covers the submission and exchange of data from clinical to post-market surveillance across all the regulators and pharmaceutical industries in Europe. One of the challenges which confronts most of the organisations is the ability to extract information from unstructured data sources such as documents. Nuances hidden in unstructured text data make it seemingly difficult and require expert curation to extract submission-relevant information manually, which is tedious, time consuming, and error prone. Therefore, application of text mining and natural language processing systems to augment and assist the experts for curation is gaining popularity in recent years. This article provides an overview of the approach taken by our organisation to enable semi-automated curation of documents relevant for IDMP submissions.

IDMP and its challenges

The European Medicines Agency (EMA) is nearing adoption of five new ISO [International Organization for Standardization] norms for the harmonised exchange of medicinal product information for products marketed in the EU and the European Economic Area (EEA) by Regulation (EU) No 520/2012. This is done via implementation of substance, product, organisation and referential (SPOR) in the identification of medicinal products (IDMP) project.¹ All marketing authorisation holders (MAHs) for marketed medicinal products for human use and sponsors of investigational medicinal products in the EU and the EEA are obliged to submit information to the EMA on any newly authorised medicines or variations to the terms of the marketing authorisation (MA), which complies with IDMP mandated standard and format. Currently product data relevant for submissions are scattered within the complex technological landscape of organisations in different systems such as regulatory information management systems (RIMS) and document management databases.² Traceability of data, varying data types (ie, structured, semi-structured and unstructured), duplicated and non-electronic formats of the data are some of the foremost challenges which most of the organisations need to deal with. In this article, we emphasise the challenges and solutions associated with unstructured text data such as submission documents.

Unstructured data relevant for the first iteration of IDMP encompass medicinal product characteristics, clinical particulars and further product information found in the summary of product characteristics (SmPC) documents. Also, in scope are the details about the manufacturers and the drug product composition which are found in Module 3 documents. Details of specific types of information present in SmPCs and Module 3 documents are explained by Schlaps (2018).³ SmPC documents for each product can range from 30 pages to more than 100 pages for products with multiple strengths and can commonly exist in multiple languages. On

the other hand, manufacturer and composition Module 3 documents are shorter, spanning one to four pages, and predominantly in English. The straightforward approach for extracting the required IDMP information from these documents would be a manual extraction. However, investment in fully manual labour to curate documents can be challenging because of:

- Long and complex documents, along with the need to map the extracted information to predefined controlled vocabulary terms and to organise the contents into the IDMP-defined data model
- The 4-eye principle (in order to ensure the highest level of quality), which requires documents to be curated at least twice, which doubles the effort
- Rotational staff with varying levels of knowledge and training which could impact consistency
- Small but relevant content variations between document versions, which might trigger a full cycle of double curation (see second point above).

Therefore, these reasons call for automation of document curation so that the system can provide baseline and uniform extraction.⁴ The machine-generated outputs can then be reviewed, corrected, and curated by experts resulting not only in speed and effort efficiencies but also improvement of quality and consistency and with minimised manual errors.

Text mining as a stimulant for IDMP

Text mining is a well-established field of science and technology that deals with the automatic extraction of valuable and meaningful information from unstructured text data sources.⁵ In the pharmaceutical and healthcare domains, applications of text mining can range from early research to find evidence to support lead discovery to post-market surveillance for understanding risk–benefits, competition, and early alerts once products are in use in the market.⁶ On a high level, application of text mining can

TABLE 1

Performance of text mining models after five rounds of iterative development and evaluation

Document type	Performance F-score (%)
SmPC English	97.8
SmPC German	97.7
SmPC French	96.4
Module 3 Composition	94.8
Module 3 Manufacturer	91.6

be categorised into: analytics and insights to find trends and patterns in the data; domain-specific sophisticated search capability to find relevant evidence for business questions; or business process automation by augmenting expert efforts for manual document curation or indexing. Hence, text mining for IDMP falls into the last category.

It is important to understand that text mining has had various levels of success in providing value to business depending on the areas of application. Research has shown that applications of text mining during early research with biomedical literature generate results that can match human accuracies. Nevertheless, machines make mistakes and their extraction quality can be significantly influenced by the document quality, the initial accuracy for the training of the text mining system and other complexities within the data. This translates into a requirement that having a text mining capability for IDMP that can match or get closer to expert accuracy is important in order to reduce the manual efforts and increase the curation throughput. Text mining models deployed for production-grade use with lower accuracy levels can create more burden than the value. Therefore, it is important to have well-defined key performance indicators that can qualify the application of text mining for IDMP and allow for performance tracking of the quality of text extraction over time.

Industrialisation of the text mining solution

The development of an accurate text mining model or algorithm is one element of the entire challenge, whereas the ability to follow proper standards and practices in order to develop and operationalise a mature product that can be used for daily business is yet another large component. This section provides a high-level overview of the process we followed for text mining system development and operationalisation.

Text mining model development

In order to develop a robust and high-quality text mining model, an iterative approach composed of model development, optimisation, and evaluation was performed. A market survey showed the existence of a variety of commercial and non-commercial solutions leveraging advanced artificial intelligence as well as linguistic rule-based systems. Every solution has its own pros and cons. For example, artificial intelligence-based solutions require tremendous “labelled” training data, which would lead to a significant time investment of business experts upfront. On the other hand, linguistic rule-based approaches require a linguistic expert to understand patterns in documents and create appropriate and scalable rules, for which a smaller amount of prepared training data is required. Considering the limited volume of “labelled” training data available, varying languages, and formats, we leveraged the linguistic rule-based solution. The initial focus was limited to documents in three languages (English, German, and French).

SmPC and Module 3 documents were sampled and segregated into five sets with ten distinct, non-overlapping documents each. This was done separately for SmPCs per language and Module 3 composition and manufacturer documents. During each of the five iterations, the text mining model was developed and optimised on the set of documents for the current and previous iterations (the training set). The model was then applied to extract information automatically from a completely unseen set of documents belonging to the next iteration (the test set). At the end of each iteration, the information extracted by the machine in the test set was manually evaluated by domain experts. Consequently, for each iteration, this process provided a benchmark of model performance as well as provided errors to model developers which they could use to improve or fine-tune the model further. The quality of the model was measured using the F-score, which is a harmonic mean of specificity and sensitivity.⁷ As a result of five rounds of iterative model development and evaluation for trilingual SmPCs and Module 3 documents, performances indicated in Table 1 were observed.

Text mining system development and operationalisation

Once a high-quality text mining model was developed, the next part of the challenge was to follow a robust methodology for system design, development, and operationalisation (Figure 1). Since the text mining for document curation embeds into business operations for regulatory submissions, we followed the GAMP 5 guidelines for establishing a compliant GxP computerised system.⁸ As indicated in Figure 1, the GAMP 5 guidelines provide an industry-standard guideline that follows a V-model for computer system development and validation (CSV model).⁹ The process recommends having at least three system-environments:

- Development environment allowing design, build and development of the system
- Validation environment, where the developed system is properly tested for technical robustness, as well as functional robustness by business users
- Production environment, which is used by business users on a day-to-day basis.

Document-deliverables and milestones for each phase are also indicated in the figure. It starts with a well-defined validation plan which describes the methodology and deliverables to validate the system. On the other hand, the qualification plan describes the methodology and deliverables to qualify the fitness of the underlying technical components and infrastructure.

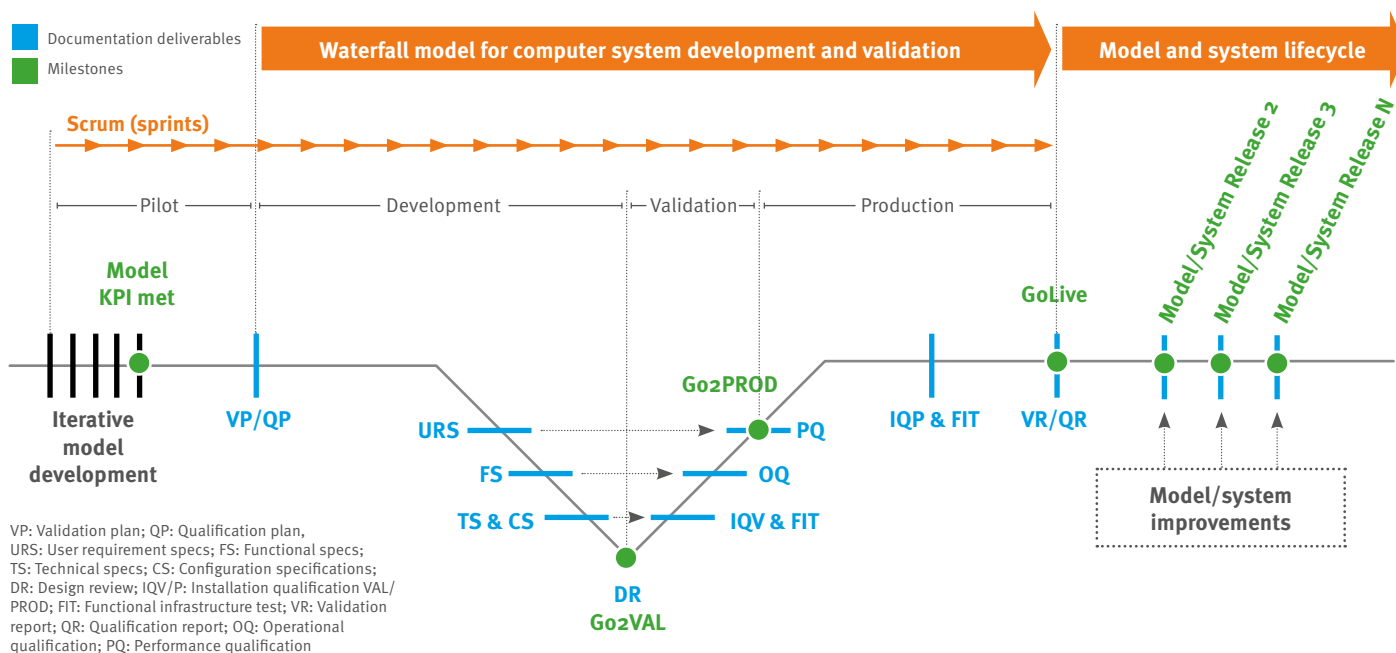
Given the fact that the CSV model is a waterfall-like model and sequential in nature, it was important to ensure agility in the entire development process. Scrum for software development is a widely adopted methodology for agile and iterative development of solutions with uncertain and varying requirements.¹⁰ Efforts were taken to combine the CSV waterfall methodology with the agile scrum methodology using three-week iterations, so-called sprints. A series of sprints was conducted to fit the sequential development, validation, and deployment, including document-deliverables and milestones as indicated in Figure 1. The overall team was set up cross-functionally to include experts from the business domain, text analytics and computer system validation during the entire project phase. Additionally, although the requirements from the IDMP perspective were well defined, we wanted to ensure agility for business users so that low-level functionalities of the system can be developed with tight feedback from the business side. Of note, once the development of the system was completed in an iterative fashion, no changes to the system were allowed during validation and production deployment phases.

A few important technology factors must be considered:

- **Enterprise security** It needs to be ensured that data storage,

FIGURE 1

End-to-end overview of IDMP text mining solution development and operationalisation



For computer system validation, a limited and important documentation deliverables and milestones have been shown.

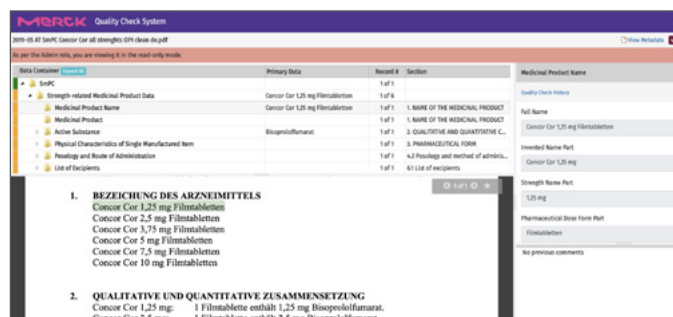
Figure adapted from Altemüller (2019)⁹

technical components, and inter-system communications are secured in line with enterprise security standards. It is important to have proper standards and practices in place for access management and data encryption, so that the confidentiality and integrity of the submission documents is achieved.

- Audit trail** Once the business users start interacting with the system, there will be continuous changes to data at different stages. For example, results of text mining are corrected and curated by users daily. It is important that audit trails are maintained which can capture business user interaction with the data (ie, who changed what and when), which can help in tracking and tracing any non-obvious observations in the data.
- Intuitive user interface (UI)** A user-friendly and ergonomic user interface is key to any successful adoption of IT systems for business processes. Figure 2 shows a quality check system (QCS) that provides business users with an interface where users can visualise actual documents (at the bottom of UI), curate text mining results (top right of the UI) and the IDMP schema (top of the UI). The QCS also entails a workflow management system where documents, after curation, can be sent for review and approval by named approvers. This feature allows the four-eye principle and ensures documents are checked by at least two different business users, if required for this document type.
- Loosely coupled design** Developing a tightly coupled software system or loosely coupled system depending on enterprise needs; both come with their own pros and cons. For example, a standalone monolithic system would have less technical interfaces to manage but comes with a burden of complexity in change management. On the other hand, the loosely coupled system encourages changes or repurposing individual components beyond the initially intended reason for development. However, they result in multiple interfaces which require additional maintenance efforts. Our system is based on loosely coupled design and technological components since our focus

FIGURE 2

Screenshot example of quality check system



was to achieve the reusability of individual components beyond the IDMP use case.

At the time of writing this article, the Merck system had gone into regular operation mode and became an integral part of the business, where it is in frequent use. As such, it is natural that new service requests arrive, for example, changes in user groups, or unexpected incidences occur, such as text mining model performance drifts, unstable system behaviour or business users requests new feature enhancement. Given the system is operated in a regulated and controlled environment, it is important that there are well-defined system management processes in place for user management, incidence management, change management, release management, evolutionary upgrades, problem management, knowledge management, and service level agreements.

System lifecycle management goes beyond standards and processes, and it requires the availability of well-trained staff including business and system owners, operations engineers, and text mining experts. Once the system is running in production mode, improvements to text mining

models are addressed by text mining experts, whereas changes to the technical components are addressed by engineers. Accountability of the service quality stays with the service delivery manager or system owner. It is necessary that a well-defined framework is available for service, system, and text mining model management and there are proper communication and common understanding between different stakeholders.

Future challenges and text mining beyond IDMP

Application of text mining for document curation and automated regulatory submissions for IDMP is an exciting journey that many organisations are pursuing. However, the lengthy journey from development of robust text mining models in the laboratory to the ability to develop an industry-grade production system within a regulated environment raises questions over investment and, ultimately, return on investment. Organisations need to balance monetary benefits against quality, compliance, and business benefits for, and beyond, IDMP.

Taking IDMP submissions as an example, future iterations of IDMP will encompass different types of document data sources to be structured, organised, and submitted. This goes beyond iteration 1 (product characteristics, composition, and manufacturer documents), and covers clinical trials, post-marketing surveillance data, and many more. It is estimated that unstructured data within enterprises outweighs structured data and therefore, the ability to reuse and repurpose text mining capabilities beyond IDMP is critical. A text mining platform that is compliant to GAMP 5 computer system validation guidelines can be a valuable asset to the data analytics capabilities of any company in the pharmaceutical domain; for example, in manufacturing intelligence (analysis of recurrent manufacturing problems), customer care intelligence (analysis of customer inquiries for product quality improvement or response streamlining),

or medical service effectiveness (analysing written communications and interviews between medical sales representatives and healthcare professionals). As such, IDMP can be therefore be perceived as a gateway into structuring the unstructured pharma data with help of text analytics. Choosing an appropriate text mining platform, having a proper system design to ensure maximum utilisation of assets, and envisioning a long-term strategy for the potential use of text mining can help enterprises maximise the benefits and mitigate the risks of investment. ■

References

1. EMA. Data on medicines (ISO IDMP standards): overview. Available at: <https://www.ema.europa.eu/en/human-regulatory/overview/data-medicines-iso-idmp-standards-overview> (accessed 16 June 2020).
2. Herrmann A, Werner J, Kloft M. Identification of medicinal products. How to turn a compliance project into a strategic initiative with additional benefits. Available at: <https://globalforum.diaglobal.org/issue/november-2019/identification-of-medicinal-products/> (accessed 16 June 2020).
3. Schlaps D. Text mining for IDMP – kill or cure? Available at: <https://www.idmp1.com/text-mining-for-idmp-kill-or-cure/> (accessed 16 June 2020).
4. Daumke P. Getting ready for IDMP. Available at: <https://averbis.com/getting-ready-for-idmp/> (accessed 16 June 2020).
5. Wikipedia. Text mining. Available at: https://en.wikipedia.org/wiki/Text_mining (accessed 15 June 2020).
6. Gurulingappa H, Karmalkar PP, Megaro G. Industry's adoption of natural language processing. Available at: http://www.pharmatimes.com/web_exclusives/industrys_adoption_of_natural_language_processing_1296256 (accessed 16 June 2020).
7. Wikipedia. F1 score. Available at: https://en.wikipedia.org/wiki/F1_score (accessed 16 June 2020).
8. ISPE. GAMP 5 guide: compliant GxP computerized systems. 2008.
9. Altemüller E. Agile in GxP CSV environments – the concept. Available at: <https://www.bpexperts.de/agilegxp> (accessed 16 June 2020).
10. Hossain E, Babar MA, Paik HY. Using scrum in global software development: a systematic literature review. In: 2009 Fourth IEEE International Conference on Global Software Engineering. 2009.

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Medical device standards update

COMPILED BY **MEHRYAR BEHIZAD**, Regulatory Director, Endomagetics Ltd

This edition of our regular column updates the progress of applicable standards to September 2020. The previous edition, submitted for publication in February 2020, missed the publication of the EU Harmonised Standards for Medical Devices which were published in March 2020. The published EU harmonised list contains a number of significant updates in terms of format.

It appears that the list has been streamlined to 288 standards which includes those standards related to active implantable medical devices and *in vitro* diagnostics (IVDs) as compared to more than 330 listed previously – a number of mainly vertical standards having been removed. The presentation format has also changed. In the new format, one document contains applicable standards to IVD and active implantable devices, as well as the core of standards applicable to medical devices in general.

The updates to the harmonised list include a number of updated editions of the standards such as ISO 11137-1, ISO 13408-2, ISO 17664:2017, ISO 10993-11. However, a significant number of standards still remain the same as those listed in the November 2017 version of the standards, even though some have been officially withdrawn. Notably, ISO 14971:2019 has not as yet been harmonised even though one of the aims for the update to this standard was better alignment with the new Medical Device Regulations which are scheduled to come into effect on 26 May

2021. By contrast, the updated version of ISO 14971 is already on the FDA consensus list. An updated version of the EU Harmonised Standards list is promised before the end of December 2020.

A number of standards (eg, ISO10993-11:2009) are now removed from both the EU harmonised list and the consensus list. As a consequence, these previous versions have been removed from this list altogether.

With respect to IVDs, the vast majority of the applicable standards outlined in the November 2017 version of the EU harmonised list still remain harmonised. However, in this edition and going forward, ISO 20776-1 has been added to the Standards Update list.

As with previous issues, the table below includes only those standards relating to medical devices and IVDs which have been subject to a change in status since the last issue of this column compiled in February 2020. In this edition it includes those standards that have now been updated in the EU harmonised list as well as those standards which were expected to be updated in the EU harmonised list but still remain to be updated. The full version of this article containing the comprehensive list of horizontal standards can be found on the TOPRA website.¹

Information on sources for this table can be found in references 2 to 7. A further update will be provided in the next edition of this column in 2021.

1. Standards – for medical devices	Status	Harmonised	FDA Consensus List	Future development, TC details or general comment
Sterilisation and sterility				
BS EN ISO 11135:2014 +A1 2019 Sterilisation of healthcare products. Ethylene oxide. Requirements for the development, validation and control for medical devices	Current	N	Y	Now on FDA consensus list. Not on EU harmonised list.
BS EN ISO 11135:2014 Sterilisation of healthcare products. Ethylene oxide. Requirements for the development, validation and control for medical devices	Now withdrawn	N	Y	Remains on FDA consensus list.
BS EN ISO 11137-1:2015 + A2 2019 Sterilisation of healthcare products – Radiation – requirements for development, validation and control for medical devices	Current	Y	Y	Now on EU harmonised list. Amendment not on FDA consensus list.
EN ISO 11138-2:2009 – Biological indicators for ethylene oxide sterilisation processes	Withdrawn	Y	N	This standard remains EU harmonised but no longer current.
EN ISO 11138-3:2009 Biological indicators for moist heat sterilisation processes	Withdrawn	Y	N	This standard remains EU harmonised but no longer current.
EN ISO 11140-1:2009 Sterilisation of healthcare products – Chemical indicators – Part 1: General requirements	Withdrawn	Y	N	This standard remains EU harmonised but no longer current.
EN ISO 11737-1:2006/AC:2009 Sterilisation of medical devices – Microbiological methods – Determination of a population of microorganisms on products	Withdrawn	Y	Y	This standard remains EU harmonised and on FDA consensus list.
EN ISO 11737-2:2009 – Tests of sterility performed in the definition, validation and maintenance of a sterilisation process	Current	Y	Y	Remains on FDA consensus list. Remains EU harmonised. Standard also applies to IVDs.
ISO 11737-2:2019 – Tests of sterility performed in the definition, validation and maintenance of a sterilisation process		N	Y	Now on FDA consensus list.

1. Standards – for medical devices	Status	Harmonised	FDA Consensus List	Future development, TC details or general comment
EN ISO 13408-2:2018 Aseptic processing of healthcare products – Filtration	Current	Y	Y	Standard also applies to IVDs. This standard is now EU harmonised.
EN ISO 13408-6:2011 +A1: 2013 – Isolator systems	Current, under review	Y	Y	Standard also applies to IVDs. A1:2013 not EU harmonised but on FDA consensus list.
EN ISO 17664:2017 Sterilisation of medical devices – Information to be provided by manufacturer for the processing of re-sterilisable medical devices	Current	Y	Y	This standard is now EU harmonised and on FDA consensus list.
ISO PRF 17664-2. Processing of healthcare products. Information to be provided by the medical device manufacturer for the processing of medical devices. Part 2. Non-critical medical devices.	Current	N	N	Status: at approval stage ISO TC198, Stage 50:20.
Biocompatibility				
ISO 10993-1:2018 Biological evaluation of medical devices – Evaluation and testing within a risk management process	Published	N	Y	On FDA consensus list but not EU harmonised.
EN ISO 10993-1:2009/AC:2010 Biological evaluation of medical devices – Evaluation and testing within a risk management process	Current, work in progress (BS EN) but withdrawn by ISO	Y	Y	Remains on FDA consensus list. Remains EU harmonised.
EN ISO 10993-3:2014 – Tests for genotoxicity, carcinogenicity and re-productive toxicity	Current, under review	Y	Y	ISO/TC 194 Stage 90.92.
EN ISO 10993-4:2017 – Selection of tests for interactions with blood	Current	N	Y	Not EU harmonised but on FDA consensus list.
EN ISO 10993-4:2009 – Selection of tests for interactions with blood	Withdrawn	Y	N	Remains an EU harmonised standard.
EN ISO 10993-5:2009 – Part 5: Tests for <i>in vitro</i> cytotoxicity	Current	Y	Y	Not EU harmonised but on FDA consensus list.
EN ISO 10993-6:2016 – Part 6: Tests for local effects after implantation	Current	N	Y	Not EU harmonised but on FDA consensus list.
EN ISO 10993-6:2009 – Part 6: Tests for local effects after implantation	Withdrawn	Y	N	Removed from FDA consensus list. Remains an EU harmonised standard.
EN ISO 10993-7:2008 Amd 1:2019 – Part 7: Ethylene oxide sterilisation residuals	Current	Y	Y	ISO/TC 194. Stage 60.60 Amd 1, now published but not EU harmonised. FDA consensus is on original 2008 version.
EN ISO 10993-9:2019 – Part 9: Framework for identification and quantification of potential degradation products	Current	N	Y	Now on FDA consensus list but not EU harmonised.
BS EN ISO 10993-10:2013 – Tests for irritation and skin sensitisation	Current, under review	N	Y	Now under review ISO/TC 194 Stage 90.92. Draft revision ready for public comment. ISO/CD10993-10 (development document) is at Stage 40.60 (close to voting).
BS EN ISO 10993-11:2018 – Tests for systemic toxicity	Current	Y	Y	Now on FDA consensus list, and EU harmonised standard
EN ISO 10993-12:2012 – Sample preparation and reference materials	Current, under review	Y	Y	Under review. ISO TC/194, stage 90.92.
ISO 10993-15:2009 – Identification and quantification of degradation products from metals and alloys	Current	Y	N	Remains EU harmonised.
ISO 10993-15:2019 – Identification and quantification of degradation products from metals and alloys	Current	N	N	Not EU harmonised.

1. Standards – for medical devices	Status	Harmonised	FDA Consensus List	Future development, TC details or general comment
EN ISO 10993-16:2017 – Toxicokinetic study design for degradation products and leachables	Current*	N	Y	Remains on FDA consensus list. Not EU harmonised. *BS version is withdrawn
EN ISO 10993-16:2010 – Toxicokinetic study design for degradation products and leachables	Withdrawn	Y	N	Remains on EU harmonised list only
EN ISO 10993-18:2009 Biological evaluation of medical devices – Part 18: Chemical characterisation of materials	Withdrawn	Y	N	Not harmonised but on FDA consensus list.
Packaging and information				
EN ISO 11607-1:2019 Packaging for terminally sterilised medical devices – Requirements for materials, sterile barrier systems and packaging systems	Current	N	Y	Not EU harmonised.
EN ISO 11607-1:2009 + A1:2014 Title as above	Withdrawn	Y	N	Remains EU harmonised. Removed from FDA consensus lists.
EN ISO 11607-2:2019 – Validation requirements for forming, sealing and assembly processes	Current	N	Y	On FDA consensus list. Not EU harmonised.
EN ISO 11607-2:2006 + A1:2014 Title as above	Withdrawn	Y	N	Remains EU harmonised. Removed from FDA consensus lists.
Information and labels				
EN 1041:2008 + A1: 2013 Information supplied by the manufacturer of medical devices	Current	Y	N	Under review – BSI CH/210/3. Draft revision ready for public comment.
Quality management and regulatory				
EN ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice	Now published by ISO	N	N	Not on consensus list and not EU harmonised.
EN ISO 14155:2011 Clinical investigation of medical devices for human subjects – Good clinical practice	Withdrawn	Y	Y	Remains EU harmonised and on FDA consensus list.
Risk management				
EN ISO 14971:2012 Medical devices – Application of risk management to medical devices	Withdrawn	Y	Y	Remains EU harmonised and on FDA consensus list.
EN ISO 14971:2019 Medical devices – Application of risk management to medical devices	Current	N	Y	Standard also applies to IVDs. Not EU harmonised but on FDA consensus list.
Statistical batch sampling				
<i>No change of standards in this field</i>				
Animal tissue utilisation in medical devices				
EN ISO 22442-1:2007 Medical devices utilising animal tissues and their derivatives – Part 1: Application of risk management	Withdrawn	Y	N	Withdrawn by ISO. Remains EU harmonised.
EN ISO 22442-1:2015 Medical devices utilising animal tissues and their derivatives – Part 1: Application of risk management	Current	N	Y	Not EU harmonised. ISO/TC 194/SC 1, Stage 90.92. On FDA consensus list only.
EN ISO 22442-2:2007 Medical devices utilising animal tissues and their derivatives – Part 2: Controls on sourcing, collection and handling	Withdrawn	Y	N	Withdrawn by ISO. Remains on EU harmonised list only.
EN ISO 22442-2:2015 Medical devices utilising animal tissues and their derivatives – Part 2: Controls on sourcing, collection and handling	Current	N	Y	Not EU harmonised. ISO/TC 194/SC 1, Stage 90.92. On FDA consensus list only.

1. Standards – for medical devices	Status	Harmonised	FDA Consensus List	Future development, TC details or general comment
Electrical and electronic safety				
BS EN IEC:60601-1-2: 2015 – Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests	Current	Y	Y	Now on FDA consensus list. Standard also applies to IVDs. Current, work in progress. Committee CH/62/1, draft of an amendment to this standard is out for approval and, if approved, has a projected publication date of Nov 2020.
Software lifecycle management				
EN IEC 62304:2006 + A1:2015 Medical device software – Software lifecycle processes	Current	Y	Y	A revision to this standard is now being drafted. Under review. Stage 60:60, ISO/TC 210. Amendment 2015 not EU harmonised but accepted on FDA consensus list. Standard also applies to IVDs.
Usability				
EN IEC 62366:2008 Medical devices – Application of usability engineering to medical devices	Withdrawn	Y	N	Standard also applies to IVDs. Now withdrawn by ISO. On EU harmonised list only. Note A1:2015. Not EU harmonised.
BS EN ISO IEC 62366-1:2015 +A1 2020 Medical devices. Application of usability engineering to medical devices (supersedes the standard above)	Current	N	Y	Current, work in progress. CH/62/1. A1 2020 now published. ISO 62366-1:2015 now withdrawn. On FDA consensus list only.
2. Standards for in vitro devices (IVDs) only	Status	Harmonised	FDA Consensus List	Future development, TC details or general comment
EN ISO 20776-1:2006 Clinical laboratory testing and IVD test systems – Susceptibility testing of infectious agents: Reference method for testing <i>in vitro</i> activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases	Withdrawn	Y	N	New to this list. EU harmonised but ISO withdrawn.
BS EN ISO 20776-1:2020 Title as above	Current	N	N	New to this list.
BS EN 61326-2-6:2006 Electrical equipment for measurement, control and laboratory use. EMC requirements. Particular requirements. IVD medical equipment	Withdrawn	Y	N	Note: 2006 version remains on EU harmonised list.
BS EN 61326-2-6:2013. Electrical equipment for measurement, control and laboratory use. EMC requirements. Particular requirements. IVD medical equipment	Current	N	N	Work in progress.

References

1. TOPRA member resources. Available at: www.topra.org/TOPRA_Member/Resources/Medical_device_resources/TOPRA/TOPRA_Member/News_Folder/2017/Resources_for_Professionals.aspx
2. Harmonised list of standards for medical devices. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=uriserv:OJ.C_.2017.389.01.0029.01.ENG
3. Harmonised list of standards for IVD devices. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=uriserv:OJ.C_.2017.389.01.0062.01.ENG
4. FDA list of consensus standards. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
5. International Organisation for Standardization (ISO) – ISO standards. Available at: www.iso.org/iso/home/standards.htm
6. ISO standard development key decision stage codes. Available at: www.iso.org/iso/stage_codes.pdf
7. European Standard Organisation. Available at: <https://standards.cen.eu/>



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GENE THERAPY

Global regulatory frameworks for the development of gene therapy products

Gene therapies have the potential to revolutionise the global healthcare system. Some of these products may offer curative benefits to patients with devastating conditions. This continuing professional development (CPD) supplement provides an overview of the regulatory framework for the development of gene therapy products in key markets.

LEARNING POINTS

- Gene therapy definitions, expedited review opportunities, and product development guidance documents differ in different jurisdictions. Developers are encouraged to review relevant guidelines and seek advice from regulators about their specific circumstances.
- Many gene therapy products are targeting rare diseases and may be eligible for orphan drug designation (ODD) with the EMA, FDA, and PMDA.
- Several countries are currently developing new regulatory frameworks dedicated to gene therapy products in order to set rules, requirements, and policies for these complex innovative therapies.
- To address developers' concerns specific to gene therapies, the EMA and the FDA published multiple guidelines and other resources, which are available on their websites.

According to recent data from the Alliance for Regenerative Medicine (ARM), there are more than 980 companies globally that are active in the development of gene therapies.¹ The landscape is expanding rapidly and, as of the end of 2019, gene therapy products are used in 1,066 ongoing clinical trials, 94 of which are Phase III trials.¹ Gene therapies have the potential to offer durable and curative, or near-curative, benefits to patients who suffer from devastating diseases; they also face unique development challenges and might need specific requirements for the quality, safety and efficacy data necessary to support a favourable benefit–risk profile. The definition of gene therapy products differs slightly dependent on jurisdictions (see Table 1).² This continuing professional development article provides an overview of global regulatory frameworks for the development of this class of complex and innovative therapies.

EU regulatory framework

The European Medicines Agency (EMA) regulates gene therapies as advanced therapy medicinal products (ATMPs) under Regulation (EC) No 1394/2007³ and Directive 2009/120/EC,⁴ which replaces Part IV of Annex I to Directive 2001/83/EC. The ATMP Regulation outlines the principles for the authorisation, supervision,

and pharmacovigilance of ATMPs; established the Committee for Advanced Therapies (CAT); and specifies financial and procedural incentives to assist in the development of ATMPs. This regulation specifies that marketing authorisation applications (MAAs) for gene therapies, as well as other ATMPs, must be evaluated under the centralised procedure.³ The CAT assesses MAAs of gene therapy products and prepares a draft opinion on their quality, safety, and efficacy, which is then provided to the Committee for Medicinal Products for Human Use (CHMP) for review. The CHMP is tasked with generating a final scientific opinion. The final opinion is then transmitted to the European Commission, which, on its adoption, issues the marketing authorisation (MA).⁵

Directive 2009/120/EC recognises the development challenges and creates a risk-based approach for evaluating MAAs for ATMPs. This approach, which is optional, is used to determine the extent of quality, nonclinical, and clinical data to be included in the MAA and to justify any deviation from the requirements of Directive 2001/83/EC. Guidance on the implementation of this approach is provided in “Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products”, and involves a four-step methodology aiming to integrate

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*Gene therapy; Advanced
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(ATMP); EMA; US FDA;
Pharmaceuticals and
Medical Devices Agency
(PMDA).*

TABLE 1

Definition of gene therapy products in the EU, US, and Japan

Jurisdiction	Name	Gene therapy definition
EMA (EU)	Gene therapy medicinal product (GTMP)	<p>“A biological medicinal product (excluding vaccines) that:</p> <p>(a) Contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence and;</p> <p>(b) Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.</p> <p>Gene therapy medicinal products shall not include vaccines against infectious diseases.”</p> <p><i>Directive 2001/83/EC, Annex I, Part IV, as amended in Directive 107 2009/120/EC</i></p>
FDA (USA)	Gene therapy product	<p>“Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified <i>ex vivo</i> for subsequent administration to humans, or may be altered <i>in vivo</i> by gene therapy given directly to the subject. When the genetic manipulation is performed <i>ex vivo</i> on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a therapeutic or prophylactic effect, or may provide a way of marking cells for later identification. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy and as such are subject to regulatory oversight.”</p> <p><i>FDA. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998</i></p>
MHLW (Japan)	Gene therapy product	<p>“The term ‘regenerative medicinal products’ (as ‘SAISEI-IRYOUTOU-SEIHIN’ in Japanese) used in this act refers to the articles (excluding quasi-drugs and cosmetics) specified in the following items which are specified by the cabinet order.</p> <p>[...]</p> <p>(2) The articles which are intended to be used in the treatment of disease in humans or animals, and are transgenic to express in human or animal cells.”</p> <p><i>Act on Pharmaceutical and Medical Devices, Chapter 1 Article 2–9</i></p>

Table adapted from Halioua-Haubold et al, “Regulatory considerations for gene therapy products in the US, EU, and Japan”.²

information systematically.⁶ Table 2 highlights the EMA guidance documents which are of relevance to ATMPs.

Many gene therapy products are targeting rare diseases, and their developers are encouraged to consider applying for an orphan drug designation (ODD). Products with an ODD receive numerous benefits including protocol assistance, a reduction in some procedural fees and, upon MAA approval, ten years of market exclusivity for the protected indication.⁷ For further details refer to a previous CPD supplement on ODDs (*Regulatory Rapporteur* October 2017).

There are multiple pathways to expedite development and approval of gene therapies in the EU, although it should be noted that there are no pathways specifically designed for ATMPs. For further details please refer to the CPD supplement on expedited pathways (*Regulatory Rapporteur* September 2020).

Micro-, small and medium-sized enterprises (SMEs) that are developing gene therapies might consider the ATMP certification procedure. This 90-days procedure, which is operated by the CAT, allows SMEs to submit either quality data alone or in conjunction with nonclinical data for scientific review. The CAT evaluates whether the data are on track to meet the standards of a future MAA. After the assessment, the CAT may

recommend the granting of a certificate, which is then issued by the EMA. The EMA website provides details on the process and on how to apply.⁸

US regulatory framework

In the US, the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Services Act (PHSA) give the FDA the legal authority to regulate medicinal products. Biologic license applications (BLAs) for gene therapy products are reviewed by the Office of Tissues and Advanced Therapies (OTAT), a division in the Center for Biologics Evaluation and Research (CBER).⁹ The contents and structure of a gene therapy investigational new drug (IND) submission is the same as any other investigational biological product,¹⁰ which are regulated under Section 351 of the Public Health Services Act.^{11,12}

In January 2020, the FDA released six final guidances for industry on manufacturing, long-term follow-up, and clinical development of gene therapy products.^{13–18} These guidances, in conjunction with several other existing guidances for gene therapy development (see Table 2), offer many insights to the FDA's current thinking in this area and provide great resources to sponsors.¹⁰

Similarly to the EU, the ODD in the US offers sponsors incentives, including tax credits for qualifying clinical

testing, waiver of application fees, and seven years of market exclusivity.^{19,20} In January 2020, the FDA also issued a new draft guidance titled “Interpreting sameness of gene therapy products under the orphan drug regulations”.²¹ According to the Code of Federal Regulations, an ODD request may be submitted for a drug that is the “same drug” of an already approved product for a rare disease or condition. Under this circumstance, the sponsor would be required to present a plausible hypothesis as to why the “same drug” was clinically superior.^{22–24} The current regulations did not specify how the “same drug” definition relates to gene therapy products, thus the draft guidance clarifies the definition of sameness in the context of gene therapies for granting ODD and eligibility for orphan drug exclusivity. Gene therapy products for the same indication of a previously approved drug may be considered different drugs in the context of ODD. The transgenes and vectors must be taken into consideration when determining the sameness of gene therapy products.

Gene therapies that address an unmet medical and are intended to treat, modify, reverse, or cure a serious or life-threatening condition may be eligible for five distinct expedited programmes that the FDA offers (fast-track, accelerated approval, priority review, breakthrough therapy and regenerative medicine advanced therapy [RMAT]). A product may receive more than one designation, though an application should be submitted for each. For further details please refer to the CPD supplement on expedited pathways (*Regulatory Rapporteur* September 2020).

Japan’s regulatory framework

In Japan, the Ministry of Health, Labour, and Welfare (MHLW) categorises and regulates gene therapy products as regenerative medical products (RMPs).²⁵ The legal framework used for these products is the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (also known as the PMD Act).^{26,27} The Pharmaceutical and Medical Devices Agency (PMDA) is responsible for evaluating RMPs both for clinical trial usage and for marketing authorisations.^{28,29} In the context of the Japanese regulatory framework, it is important to distinguish between RMPs and regenerative medicines, which is a separate category that is exempt from market approval. The Act on the Safety of Regenerative Medicines (ASRM) regulates the use of regenerative medicines in the course of clinical practice or as part of clinical research not conducted to support registration.³⁰

Japan regulates the risks associated with the use and release of living modified organisms (LMOs) in accordance with the Cartagena Protocol.³¹ Under the Cartagena Act, any organism with inserted, extracellularly processed nucleic acid is regarded as an LMO and is subject to the regulations of the Act.³² The MHLW in conjunction with the Ministry of the Environment review applications submitted by technology users which outlines the details of production and any knowledge

of potential impacts on biodiversity. These applications must be approved prior to the use of gene therapy products in Japan, along with any other clinical trial approval requirements.³³

As with all other types of products, gene therapy Japanese marketing applications are reviewed by the PMDA, which performs a scientific review and prepares a review report in consultation with external experts. The MHLW performs its own review, including further consultation with different external experts, and is then responsible for approving the marketing authorisation.^{34,35}

Similarly to the EU and the US, the PMDA provides a priority consultation system for ODD products.³⁶ Products also qualify for an extended reexamination period of ten years, compared to seven years for non-ODD products. The target review time for MAAs is nine months. Subsidies and preferential tax treatment are also available.³⁷

However, unlike the US and EU, the Japanese expedited framework does not specify requirements for diseases’ severity or the patient population, nor makes comparisons with existing treatments.³⁸ In Japan, particular attention has been given to the SAKIGAKE, or “pioneer” designation system. SAKIGAKE designation provides substantial benefits, including appointment of a PMDA manager or “concierge”, substantial preapplication consultation, prioritised consultation, and prioritised review timeline with a total target time of six months.³⁹ Products must be expected to demonstrate prominent effectiveness in a serious disease, and a marketing authorisation must be submitted in Japan first or simultaneously with other first MAAs in other jurisdictions.⁴¹

For more information on SAKIGAKE designation, see *Regulatory Rapporteur* February 2019.

Under the PMD Act, regenerative medicine products also may qualify for conditional and time-limited approval. Under this conditional approval, a product is authorised for a certain amount of time if safety has been confirmed in Phase I or Phase II trials and efficacy can be assumed from the same trials. Efficacy must be demonstrated in confirmatory trials to be conducted while the product is conditionally approved and an application for full approval submitted in a pre-specified time period not longer than seven years.^{41,42}

Other countries

Several countries are currently working on establishing regulatory frameworks for gene therapies, with two key examples being Canada and Brazil. Currently, Health Canada does not have specific regulations dedicated to gene therapy products, and these products are regulated as drugs under the Food and Drug Regulations in Canada. However, Health Canada is proposing the creation of a new, flexible regulatory pathway commonly called the Regulatory Sandbox. This framework would allow for creating custom criteria for the authorisation of individual advanced therapy products. On further

TABLE 2

Key gene therapy guidances for EMA and FDA

Agency	Key guidance documents
FDA	<ul style="list-style-type: none"> Interpreting sameness of gene therapy products under the Orphan Drug Regulations; draft Guidance for industry – January 2020 Chemistry, manufacturing, and controls (CMC) information for human gene therapy investigational new drug applications (INDs); guidance for industry – January 2020 Long-term follow-up after administration of human gene therapy products; guidance for industry – January 2020 Testing of retroviral vector-based human gene therapy products for replication competent retrovirus during product manufacture and patient follow-up; guidance for industry – January 2020 Human gene therapy for hemophilia; guidance for industry – January 2020 Human gene therapy for rare diseases; guidance for industry – January 2020 Human gene therapy for retinal disorders; guidance for industry – January 2020 Evaluation of devices used with regenerative medicine advanced therapies; guidance for industry – February 2019 Expedited programs for regenerative medicine therapies for serious conditions; guidance for industry – February 2019 Recommendations for microbial vectors used for gene therapy; guidance for industry – September 2016 Design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products; guidance for industry – August 2015 Considerations for the design of early-phase clinical trials of cellular and gene therapy products; guidance for industry – June 2015 Determining the need for and content of environmental assessments for gene therapies, vectored vaccines, and related recombinant viral or microbial products; guidance for industry – March 2015 Guidance for industry: preclinical assessment of investigational cellular and gene therapy products – November 2013 Guidance for industry: potency tests for cellular and gene therapy products – January 2011 Guidance for industry: guidance for human somatic cell therapy and gene therapy – March 1998
EMA	<ul style="list-style-type: none"> Development and manufacture of lentiviral vectors – May 2005 Non-clinical testing for inadvertent germline transmission of gene transfer vectors – May 2007 Non-clinical studies required before first clinical use of gene therapy medicinal products – May 2008 Scientific requirements for the environmental risk assessment of gene-therapy medicinal products – May 2008 Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products – January 2009 Follow-up of patients administered with gene therapy medicinal products – May 2010 Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells – May 2012 Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products – February 2013 Quality, preclinical and clinical aspects of gene therapy medicinal products – July 2018 Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials – January 2019

evaluation, longer term regulations and policies may be established after an assessment of the benefits and limitations of the regulatory sandbox is performed. Brazil's National Health Surveillance Agency (ANVISA), similarly to other jurisdictions, also classifies gene therapy products as ATMPs. ANVISA recognised the challenges in regulating gene and cell therapies and created a committee of experts called the Chamber for Advanced Cell Therapy (CAT).⁴³ This committee advises ANVISA in regulations for cell and gene therapies, regulation of ATMP clinical trials, and also supports the agency in the review of ATMP products.^{44,45}

Conclusions

The development of new gene therapy products is a rapidly growing sector, as evidenced by the scientific, clinical and financial advancements of recent years. It is strengthened by a solid stakeholder support from not only industry experts, but regulators, lawmakers, providers, and patient advocates. Many patients are poised to benefit from these new complex and innovative therapies in the coming decades. The work of regulatory affairs professionals will be vital while

we contribute to continue building the infrastructures necessary to develop and deliver them. ■

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DISCLAIMER: The content of this article represents the individual opinions of the authors and may not necessarily represent the views of their employers.

References

Note: The references listed below include those cited in the Case Study on page 6.

- Lambert JL. State of the industry: the financial, clinical, and scientific landscape for cell and gene therapies. *Cell & Gene Therapy Insights*. 2020;6(1):47–54.
- Halioua-Haubold, Peyer JG, Smith J et al. Regulatory considerations for gene therapy products in the US, EU, and Japan. *Yale Journal of Biology and Medicine* 2017;90:683–693.
- Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal L324* p121–137. Available at: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:00121:00137:EN>

- do?uri=OJ:L:2007:324:0121:0137:en:PDF (accessed 21 May 2020).
4. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products; Official Journal L242 p3–12. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2009_120/dir_2009_120_en.pdf (accessed 21 May 2020).
5. Detela G, Lodge A. EU Regulatory pathways for ATMPs: standard, accelerated and adaptive pathways to marketing authorisation. *Molecular Therapy: Methods & Clinical Development*. 2019;13:205–232.
6. EMA. Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products. 2013. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf (accessed 21 May 2020).
7. EMA. European Medicines Agency: orphan incentives. Available at: www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives (accessed 25 March 2020).
8. Certification procedures for micro-, small- and medium-sized enterprises (SMEs). Available at: www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/advanced-therapy-development/certification-procedures-micro-small-medium-sized-enterprises-smes (accessed 21 May 2020).
9. FDA. CBER Product Jurisdiction. Available at: www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/cber-product-jurisdiction (accessed 21 May 2020).
10. FDA. Guidance for human somatic cell therapy and gene therapy, guidance for industry. FDA. 1998. Available at: www.fda.gov/media/72402/download (accessed 21 May 2020).
11. 42 U.S.C § 262 (2010).
12. FDA. Frequently asked questions about therapeutic biological products. Available at: <https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products> (accessed 21 May 2020).
13. FDA. Chemistry, manufacturing, and control (CMC) information for human gene therapy investigational new drug applications (INDs); guidance for industry. 2020. Available at: www.fda.gov/media/113760/download (accessed 21 May 2020).
14. FDA. Long term follow-up after administration of human gene therapy products; guidance for industry. 2020. Available at: www.fda.gov/media/113768/download (accessed 21 May 2020).
15. FDA. Testing of retroviral vector-based human gene therapy products for replication competent retrovirus during product manufacture and patient follow-up; guidance for industry. 2020. Available at: www.fda.gov/media/113790/download (accessed 21 May 2020).
16. FDA. Human gene therapy for hemophilia; guidance for industry. 2020. Available at: www.fda.gov/media/113799/download (accessed 21 May 2020).
17. FDA. Human gene therapy for rare diseases; guidance for industry. 2020. Available at: www.fda.gov/media/113807/download (accessed 21 May 2020).
18. Human gene therapy for retinal disorders; guidance for industry. 2020. Available at: www.fda.gov/media/124641/download (accessed 21 May 2020).
19. 21 U.S.C. § 379 (2010).
20. FDA. Prescription Drug User Fee Act waivers, reductions, and refunds for drug and biological products guidance for industry. 2019. Available at: www.fda.gov/media/131797/download (accessed 21 May 2020).
21. FDA. Interpreting sameness of gene therapy products under the orphan drug regulations. Available at: www.fda.gov/media/134731/download (accessed 21 May 2020).
22. 21 C.F.R. § 316.20 (2016).
23. Hong P, Sarpatwari A, Kesselheim AS. Orphan drug designation and exclusivity for “same drugs”. *The Journal of Law, Medicine & Ethics*. 2019;47(2):34–349.
24. 21 U.S.C. § 360cc (2010).
25. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Act No. 145 of August 10, 1960, as last amended by Act No. 50 of 2015; Translation from the Japanese Law Translation Database System, Ministry of Justice. Available at: www.japaneselawtranslation.go.jp/law/detail/?ft=1&re=02&dn=18x=34&y=14&co=01&ia=03&ja=04&ky=the+law+on+securing+quality%2C+efficacy+and+safety+of+products+including+pharmaceuticals+medical+devices&page=1 (accessed 21 May 2020).
26. Asahara H. Global focus: Japan’s regenerative medicine regulatory pathways: encouraging innovation and patient access. Food and Drug Law Institute. March 2019. Available at: www.fdl.org/2019/02/global-focus-japans-regenerative-medicine-regulatory-pathways-encouraging-innovation-and-patient-access/ (accessed 21 May 2020).
27. Hara A, Sato D, Sahara Y. New governmental regulatory system for stem cell-based therapies in Japan. *Ther Innov Regul Sci*. 2014;48:681–688.
28. Pmda.go.jp. PMDA: outline of reviews and related services. Available at: www.pmda.go.jp/english/review-services/outline/0001.html (accessed 25 March 2020).
29. Sato D. Updates on global movement in regulation of advanced therapeutics [PowerPoint presentation]. Available at: www.pmda.go.jp/files/000209780.pdf (accessed 25 March 2020).
30. Institutional framework for promoting the future implementation of regenerative medicine [Powerpoint presentation]. Available at: www.mhlw.go.jp/english/policy/health-medical/medical-care/dl/150407-01.pdf (accessed 25 March 2020).
31. biodic.go.jp. Ministry of the Environment: biosafety regulations in Japan. Available at: www.biodic.go.jp/bch/english/cartagena/index.html (accessed 25 March 2020).
32. Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003). Available at: www.env.go.jp/en/laws/nature/act_csubdlrmo.pdf (accessed 21 May 2020).
33. Tsuda M, Watanabe KN, Ohsawa R. Regulatory status of genome-edited organisms under the Japanese Cartagena Act. *Front. Bioeng. Biotechnol*. 2019;7:387.
34. pmda.go.jp. Pharmaceutical and Medical Devices Agency: drugs review. Available at: www.pmda.go.jp/english/review-services/reviews/0001.html (accessed 25 March 2020).
35. Sumimasa N, Ozawa K. New Japanese regulatory frameworks for clinical research and marketing authorisation of gene therapy and cellular therapy products. *Current Gene Therapy*. 2017;17(1):17–28.
36. Mhlw.go.jp. Ministry of Health, Labor and Welfare. Overview of orphan drug/medical device designation system. Available at: www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html (accessed 21 May 2020).
37. Regulatory updates in Japan [PowerPoint Presentation]. Available at: www.pmda.go.jp/files/000226208.pdf (accessed 21 May 2020).
38. Jokura Y, Yano K, Yamato M. Comparison of the new Japanese legislation for expedited approval of regenerative medicine products with the existing systems in the USA and European Union. *Journal of tissue engineering and regenerative medicine*. 2018;12(2):e1056–e1062.
39. Strategy of SAKIGAKE. Available at: www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-01.pdf (accessed 21 May 2020).
40. Strategy of SAKIGAKE as a package [PowerPoint presentation]. Available at: www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-02.pdf (accessed 25 March 2020).
41. Regulatory update from MHLW/PMDA [PowerPoint presentation]. Available at: www.pmda.go.jp/files/000221880.pdf (accessed 25 March 2020).
42. Kenji K. Regulatory frameworks of regenerative medicines and products review in Japan [PowerPoint presentation]. Available at: www.pmda.go.jp/files/000226121.pdf (accessed 25 March 2020).
43. ANVISA. Ordinance 1700 of December 12, 2012.
44. ANVISA. Ordinance 1731 of September 9, 2016.
45. Galli MC, Serabian M, editors. *Regulatory aspects of gene therapy and cell therapy products*. 1st ed. New York: Springer International Publishing; 2015.
46. EMA. Assessment report YESCARTA; CHMP; 22 June 2018. Available at: www.ema.europa.eu/en/documents/assessment-report/yescarta-epar-public-assessment-report_en.pdf (accessed 21 May 2020).
47. FDA. Food and Drug Administration: BLA clinical review memorandum. Available at: www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (accessed 25 March 2020).
48. FDA. BLA approval. Available at: www.fda.gov/media/108458/download (accessed 21 May 2020).
49. Yescarta prescribing information. Available at: www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---YESCARTA.pdf (accessed 21 May 2020).
50. FDA. Food and Drug Administration: risk evaluation and mitigation strategy (REMS) memorandum. Available at: www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (accessed 25 March 2020).
51. EMA. Yescarta summary of product characteristics. Available at: www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf (accessed 21 May 2020).

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CASE STUDY

Gene therapy: regional assessment comparison

Axicabtagene ciloleucel (tradename YESCARTA) is an autologous chimeric antigen receptor T-cell (CAR-T) therapy that targets CD19 and is approved for the treatment of aggressive, relapsed or refractory forms of B-cell non-Hodgkins lymphoma (NHL). The active substance is composed of a patient's cells that have undergone *ex vivo* modification, which causes the T-cells to express an anti-CD19 directed CAR. CD19 is expressed as a surface antigen in diffuse large B-cell lymphoma (DLBCL) and other aggressive B-cell lymphomas. These transduced T-cells are reinfused back into the patient from which they were taken, meaning that each infusion of axicabtagene ciloleucel is unique to each patient.^{46,47}

Primary efficacy data for the EU and US submissions came from study KTE-C19-101 (ZUMA-1), which was a single-arm, open-label, multicentre Phase I/II trial with two segments. In this study, 101 patients received an infusion of the intended dose of ~2x10⁶ cells/kg of body weight. Patients had previously received an anti-CD20 monoclonal antibody and anthracycline. The primary efficacy endpoint was objective response rate per investigator and was also assessed by an independent review committee (IRC). Supportive safety data were provided from additional single-arm, open-label studies of doses ranging from ~0.5-2x10⁶ cells/kg of body weight. Significant risks were also identified, including cytokine release syndrome (CRS) and neurologic toxicities, including fatal cases.^{46,47}

Regulatory history and review

The EMA granted ODD for Yescarta for DLBCL, primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma (FL). Eligibility to PRIME was granted in May 2016 based on data from the ZUMA-1 study and from a separate, open-label Phase I study. An accelerated assessment procedure was agreed on in June 2017, and the MAA submitted in July 2017. During the assessment, the CAT concluded that it was no longer appropriate to maintain the accelerated assessment procedure, due to the adoption of a substantial list of questions and the need for a GCP inspection during the procedure. In June 2018, the CAT and the CHMP concluded that the efficacy demonstrated in the ZUMA-1 trial was sufficient to warrant approval. Comparisons were drawn to the retrospective global patient-level pooled study Scholar-1 in patients with aggressive forms of NHL. A post-authorisation safety study (PASS) was required to better characterise the safety profile in the post-marketing setting. The EMA also required steps to certify administration sites, including healthcare professional (HCP) training, patient education, and the availability of tocilizumab on site in order to manage any potential CRS occurrences.⁴⁶

US regulatory history and review

In the US, axicabtagene ciloleucel was granted ODD for DLBCL (March 2014), as well as for PMBCL and FL (April 2016). Breakthrough therapy designation for refractory aggressive

NHL was granted in December 2015. At a pre-BLA meeting in October 2016, the OTAT informed the sponsor that follow-up efficacy data longer than six months from the pivotal study would be needed to support the BLA. There were also fewer than the pre-specified number of subjects in the primary analysis. The sponsor initiated a rolling submission in December 2016. In May 2017, the FDA addressed the inadequacy of the follow-up duration in both the submitted data cuts; agreement was reached to submit updated efficacy data, which was completed in June 2017. At that point the FDA granted the BLA priority review. The agency did not request input from an advisory committee.

The FDA efficacy review noted concerns regarding the interpretability of results for time-to-event endpoints due to the open-label nature of the pivotal study. The FDA recommended that primary efficacy per the IRC be prioritised for regulatory decisions. Limitations were noted regarding the evaluation of duration of response due to a high amount of censoring of data before six months.⁴⁸ In October 2017, the FDA granted full approval of the BLA.⁴⁸ The summary basis of approval highlights the adequate number of trial participants evaluated, the magnitude and durability of the treatment effect, and the high level of unmet medical need. Notably, a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) was deemed necessary. This REMS included a boxed warning concerning CRS and neurologic toxicities.⁴⁹ Administration site certification activities, including prescriber training and availability of tocilizumab, were included as requirements.⁵⁰ An observational study was required as a PMR to assess the long-term safety.⁴⁸

Japan regulatory history and review

On 31 March 2020, a new drug application was submitted to the MHLW for review. In addition to the data packages submitted in the US and Europe, the Japanese submission included the results of a Phase II bridging study in Japanese patients with relapsed/refractory B-cell lymphomas.

Conclusions

Both EU and US regulators expressed an interest in understanding the durability of effect.^{46,47} Although data from an open-label study were used as the primary evidence of efficacy, the FDA clinical reviewer recommended that regulatory decisions focus on the results from the IRC rather than investigators. The conclusions were largely similar between the two agencies, with both requiring post-marketing assessment of the long-term safety of the product and specific risk-mitigation measures to certify sites to administer the product. Approved product labelling in the EU describes findings from the retrospective meta-analysis SCHOLAR-1.⁵¹ Although this meta-analysis was also submitted in the US BLA, it is not referenced or discussed in the USPI.^{47,49} We await the Japanese assessment to determine their focus. ■

Quiz: Test your knowledge

Now you have read the supplement, complete the following self-assessment exercise either for your own satisfaction or more formally by going to topra.org/CPDsupplements and answering the questions online. Successful completion and submission of the assessment form means that you can claim your lifelong learning (LLL) hour for the task, which members can add to their CPD recording tool.

MCQs (complete the quiz online at http://bit.ly/RR_CPD)

1. The EU ATMP Regulation:

- ☐ A. Outlines the principles for the authorisation, supervision, and pharmacovigilance of ATMPs
- ☐ B. Established the Committee for Advanced Therapies (CAT)
- ☐ C. Specifies financial and procedural incentives to assist in the development of ATMPs
- ☐ D. All of the above

2. Under the Cartagena Act in Japan, regenerative medicine products may qualify for conditional approval. Is this:

- ☐ A. True
- ☐ B. False

3. The FDA guidance on “Expedited programs for regenerative medicine therapies for serious conditions” provides information about five pathways to expedite patient access to new gene therapy products that address an unmet medical need in the treatment of a serious or life-threatening condition. Is this:

- ☐ A. True
- ☐ B. False

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